ANNALS OF SURGERY

VOL. 114 SEPTEMBER, 1941 No. 3

EXPERIMENTAL CEREBRAL TRAUMA

III. THE EFFECTS OF ACUTE UREMIA, OF VENOUS OBSTRUCTION, OF HYPERTHERMIA, AND OF INTENSIVE IRRADIATION ON THE WATER CONTENT OF THE DOG'S BRAIN

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IN PREVIOUS EXPERIMENTAL STUDIES,[1, 2] it has been found that the water content of the dog's brain is remarkably constant in normal animals. Further, no significant alteration in the water content of cerebral gray or white matter, cerebellar gray matter or the brain stem was produced by trauma to the head, even though the trauma was sufficiently severe to produce a marked elevation in cerebrospinal fluid pressure, and even though in some experiments a portion of the skull and dura mater was left open to allow free expansion of the brain. The findings in these previous experiments are summarized in Table VII.

The series of experiments to be reported in this paper were undertaken to determine whether the water content of the brain was altered in other conditions which have been reported to be associated with "cerebral edema." The conditions studied were acute uremia, obstruction of the superior vena cava and azygos vein, severe fever, and intensive irradiation of the head.

Methods and Results.—Dogs were used in all experiments and the same methods of study of the water content of the brain were employed as in the previously reported experiments.[1, 2] The animal was sacrificed by stabbing the heart. The brain was removed and specimens of cerebral gray and white matter, cerebellar gray matter, and brain stem were obtained by the same individual (C. P.) and by the same technic in all experiments. Specimens were weighed immediately (seven to ten minutes after death) and dried to constant weight at 60° C.

Group I.—Acute Uremia: Bilateral nephrectomy was performed in six

and bilateral ureteral ligation in five animals, under nembutal anesthesia. Such animals go into prompt and profound uremia.[3] They were sacrificed by stabbing the heart in the moribund period two to five days after operation. In the nephrectomy group, mean arterial blood pressure was determined with the animal at rest before operation and immediately before sacrifice by means of a needle inserted into the femoral artery and communicating with a mercury manometer. Blood nonprotein nitrogen was determined at the same time in both groups, the eyegrounds were examined, and the cerebrospinal fluid pressure determined* by means of a needle in the cisterna magna immediately before the animals were sacrificed.

TABLE I

THE EFFECTS OF BILATERAL NEPHRECTOMY

		Mean Blood Pressure		Blood Nonprotein Nitrogen		Percentage of Water in Brains			
Dog No.	Days After Operation	Control Mm.Hg.	Immediately Before Sacrifice Mm.Hg.	Control Mg. Per Cent	Immediately Before Sacrifice Mg. Per Cent	Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E1	3	160		34	109	80.0	64.4	80.6	71.8
E2	2	160	110	31.5	109	79.7	64.1	79.5	70.3
E3	2	120	90	30	110	79.7	68.2	79.0	71.3
E5	2	100	90	31		78.6	66.8	79.2	70.6
E6	3	80	80	32	114	79.2	67.0	79.3	72.0
E7	3	60	50	30	112		69.2		71.0
Averages						79.4	66.6	79.5	70.2

All animals subjected to bilateral nephrectomy exhibited lethargy and drowsiness progressing into deep stupor. They took little or no water. None had convulsions or other symptoms referable to the nervous system. Other findings are given in Table I. The blood pressure diminished from 160 to 110 Mm. in one animal, and remained essentially unchanged in the remaining experiments. The blood nonprotein nitrogen was greatly elevated in five cases† at the termination of the experiments. The brain appeared normal in all animals except Dog E6, in which it seemed somewhat shrunken after the dura was opened. Values for the water content of cerebral and cerebellar gray matter and brain stem were remarkably constant. Those for the cerebral white matter were more variable and were definitely lower than average normal figures in two experiments (Dogs E1 and E2). Average values, however, were very close to normal averages (Table VII).

The animals in which both ureters were ligated were sacrificed after three to five days. Two exhibited convulsions and two vomited frequently. None drank water after the first day. The blood nonprotein nitrogen was

* The needle was connected directly with a water manometer. With the head slightly elevated and the neck flexed anteriorly, cerebrospinal fluid normally barely appears in the manometer. Any measurable rise in the tube was assumed to be an elevation of pressure above the normal.

† The blood specimen from Dog E5 clotted and was discarded.

over 200 mg. per cent in all cases and the cerebrospinal fluid pressure was slightly elevated in two animals (Table II). The brains were grossly normal. The water content of the cerebral gray matter was slightly but consistently lower than the normal value. That of the cerebral white matter was somewhat variable and was definitely low in two animals. The other values were consistently normal.

TABLE II

THE EFFECT OF BILATERAL URETERAL LIGATION

		Findings Immediately Before Sacrifice			Percentage of Water in Brains			
Dog No.	Days After Operation	Blood N.P.N. Mg. Per Cent	CSF Pressure (Cisternal)	Optic Disks	Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E26	5	200	±	Normal	77.6	65.7	78.3	71.4
E27	3	250	±	Normal	78.5	67.9	79.8	70.7
E28	3	205	±	Normal	78.7	67.0	78.6	70.1
E29	3	230	>10 Mm. increase	Normal	78.3	66.5	80.8	71.4
E30	3		>10 Mm. increase	Normal	78.6	63.6	78.8	69.2
Averages					78.3	66.1	79.3	70.6

COMMENT.—The neurologic symptoms occurring so frequently in uremia have long been attributed to "cerebral edema." Rees[4] and Traube[5] believe that cerebral edema was the cause of such symptoms, and Volhard[6] postulated an "acute false uremia" which he thought due to cerebral edema. Fishberg[7] states that this cerebral edema is the result (and not the cause) of "hypertensive encephalopathy," with or without uremia. Blackfan[8, 9] has repeatedly emphasized the presence of cerebral edema in uremia in children.

The "acute" experiments reported above are not directly comparable to such clinical states, but they serve to cast doubt upon the occurrence of increased cerebral tissue fluid in acute uremia. The low fluid values found in some of our experiments may be the result of vomiting and fluid deprivation.

Group II.—Venous Obstruction: In four dogs, the superior vena cava was ligated, and in four others, both the superior vena cava and the azygos vein were ligated. Operations were performed under intratracheal, positive pressure, ether anesthesia. In the former four experiments, the animals were sacrificed two to 14 days after operation. In the latter, the animals immediately became very ill and were sacrificed 24 to 36 hours after operation. Cerebrospinal fluid pressure was measured by means of a needle in the cisterna magna (with the head in the same position as in previous experiments), and the eyegrounds were examined before sacrifice. Complete necropsy, in addition to removal of brain specimens, was performed after death. In all cases, the ligatures had been properly placed and the venous obstruction remained as intended. The animals were sacrificed and specimens of brain tissue were removed and studied as before.

When the superior vena cava alone was ligated, the animals showed little general or local effect. In two of the four experiments, a moderate effusion of serosanguineous fluid occurred in the right pleural cavity. Edema of the

scalp and papilledema did not occur. The water content of the brain closely approximated normal values except for some variations in the cerebral white matter (Table III).

TABLE III

THE EFFECTS OF LIGATION OF THE SUPERIOR VENA CAVA

Dog No.	Time of Sacrifice, Days After Operation	Percentage of Water in Brains: Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E13	2	80.3	65.7	80.3	71.6
E12	7	80.0	70.0	80.1	71.6
E14	7	79.5	66.4	80.2	70.4
E15	14	80.3	70.8	78.2	73.2
Averages		80.0	68.2	79.7	71.7

On the other hand when both the superior vena cava and azygos vein were ligated, profound alterations in the animals' general condition were observed. It was necessary to sacrifice them at the end of 24 hours (three dogs), or 36 hours (one dog), because of extreme apathy or stupor and impending death. There was marked edema of the scalp (with subperiosteal hemorrhage in one instance). The optic disks were very hyperemic in one dog, and frankly choked in two others. No retinal or intracranial hemorrhages were observed. The cerebrospinal fluid pressure was elevated in all experiments, the smallest elevation being 20 Mm., the largest 125 Mm. of water. In one animal, a large amount of milky fluid filled the pleural cavities.*

Brain water values are shown in Table IV. In one animal (Dog E16), the water content of the cerebral and cerebellar gray matter was elevated significantly. In the remaining instances, all values were approximately normal, as were the averages.

TABLE IV

THE EFFECTS OF LIGATION OF THE SUPERIOR VENA CAVA AND AZYGOS VEIN

Dog No.	Time of Sacrifice, Days After Operation	Percentage of Water in Brains: Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E16	1	82.2	70.7	81.1	72.2
E17	1	79.2	69.0	79.3	71.5
E18	1	79.1	68.7	79.7	70.0
E19	1½	79.2	66.2	79.4	69.2
Averages		79.9	68.6	79.9	70.7

COMMENT.—Although the superior vena cava has been experimentally ligated by several investigators,[10, 11, 12] the cerebral effects of the procedure have not been studied. That clinical neurologic symptoms may result from obstruction of the superior vena cava (by tumors, aneurysms, *etc.*) has long been recognized. These symptoms were attributed merely to venous stasis

* Similar chyle-containing fluid has been found in the pleural cavities of cats after ligation of the superior vena cava by Blalock and his associates.[10, 11]

by Phillips,[13] and Lilienthal,[14] but Ehrlich, Ballon, and Graham[15] stated: "The venous stasis may also cause cerebral symptoms because of edema in the meninges and brain substance." The brain was not examined in the necropsy reported by the last-named authors. Waterfield[16] reported marked elevation of the cerebrospinal fluid pressure in a patient with clinical evidence of obstruction of the superior vena cava.

No direct observations of cerebral edema in the presence of distant venous obstruction have been found in the literature. The high venous pressure which produces edema of the scalp, papilledema and elevated cerebrospinal fluid pressure, might well be expected to produce edema of the brain as well. However, no evidence of such edema was found.

An increased intracranial blood volume must certainly have existed in these experiments and this could account for the elevation of intracranial pressure. The observations of Shapiro and Jackson,[17] which were discussed in the preceding paper in this series,[2] are of interest in this connection. These authors believe that the increased pressure resulting from cerebral trauma is due to increased intracranial blood volume (intravascular and extravascular). This possibility was also suggested in the first paper of this series.[1]

Group III.—Fever: In four experiments, the dogs were placed in an hyperthermic chamber, the temperature of which was maintained at 48–52° C. They remained in the chamber one to one and one-quarter hours. Specimens of brain were obtained as usual immediately after removal.

All animals were severely prostrated by the time of removal from the hyperthermic chamber. Panting was marked and salivation very profuse in all instances. Rectal temperature on removal was 44.4° to 45.5° C. (112° to 114° F.). Dogs E8 and E9 had generalized convulsions one and one-quarter hours after being placed in the chamber and expired suddenly when removed immediately afterward. Dogs E10 and E11 also had repeated convulsions before removal, but were removed and sacrificed one-quarter hour sooner. The cerebrospinal fluid pressure was normal in both animals immediately after removal. At necropsy, the brains presented no visible abnormality.*

The brain fluid findings are shown in Table V. The percentage of water in both cerebral and cerebellar gray matter, and in the brain stem was consistently higher than normal in all experiments. In the cerebral white matter, the percentage of water was within normal limits.

COMMENT.—In 1918, McKenzie and LeCount[18] reported an increase in the water content of the brains of patients dying of heat stroke. Objections to the validity of these findings have previously been mentioned.[1] Numerous other authors have reported finding cerebral edema in patients dying of heat stroke or following artificial fever therapy (Lichtenstein,[19] Watts,[20] Hartman,[21] Schnabel and Fetter,[22] and Chunn and Kirkpatrick[23])—but these findings are based on the gross and microscopic appearance of the brains

* "Petechial hemorrhages" noted in the protocol of one experiment proved to be blood vessels (distended?) on microscopic study.

and not on water determinations. In their report of a careful experimental study, Hall and Wakefield[24] did not report gross edema. Microscopically, they found swelling of the cytoplasm of glial cells.

TABLE V

THE EFFECTS OF HYPERTHERMIA

Dog No.	Temp. of Hypertherm.	Rectal Temp. on Removal	Hours in Hyper-therm.	Percentage of Water in Brains: Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E8	48° C.	44.4° C.	1¼	80.3	67.6	80.4	72.3
E9	48° C.	45.0° C.	1¼	81.3	66.1	81.3	72.8
E10	52° C.	45.0° C.	1	80.1	67.0	80.7	71.7
E11	52° C.	45.5° C.	1	82.6	67.8	82.4	73.2
Averages				81.1	66.7	81.2	72.5

In our experiments, the uniformly high values for water content of cerebral and cerebellar gray matter and brain stem seem to us to be significant. It is thought justifiable to conclude that true edema of these portions of the brain results from extreme hyperpyrexia.

Group IV.—Intensive Irradiation of the Head: In six experiments, deep roentgen radiation was administered to the entire head. A dosage of 3,000 roentgen units (with backscatter) was delivered in each animal.* The animals were sacrificed at the end of 24 hours in two experiments, 48 hours in one experiment, 21 days in two experiments, and 90 days in one experiment. The eyegrounds were examined and cerebrospinal fluid pressure determined immediately prior to sacrifice.

In the two animals sacrificed one day, and the one sacrificed two days after irradiation, no significant abnormality was noted in appearance of the scalp, optic disks or brain. The cerebrospinal fluid pressure was slightly elevated (less than 10 Mm. H_2O) in one experiment (Dog E25), but not at all in the other.

In the animals sacrificed after longer intervals, the scalps were ulcerated and edematous, but the optic disks and brain were not abnormal in appearance. In Dog E24, an elevation of cerebrospinal fluid pressure of less than 10 Mm. of H_2O was noted.

The percentage of water in the brain specimens varied somewhat more than usual in the individual experiments (Table VI), but the average findings showed no significant variation from normal values.

COMMENT.—The production of edema by irradiation therapy of brain tumors has long been assumed. The literature on this subject was summarized by Bailey, Sosman, and Van Dessel,[25] and the danger of edema has more recently been reiterated by Alpers and Pancoast.[26] In describing the effects of experimental radium implantation in the brains of dogs, Pendergrass,

* We are indebted to Dr. Herbert Francis, of the Department of Radiology, for administration of the radiation and for the following description of technic: 200 kv., 20 ma., 50 cm. distance. ½ Mm. Cu., 1 Mm. Al. filters.

Hayman, Houser and Rambo[27] stated: "The brain . . . shows a general swelling throughout the entire radiated hemisphere, which . . . must be ascribed to the production of an edema which is not limited to the radiated area, but extends throughout the entire hemisphere."

TABLE VI

THE EFFECTS OF INTENSIVE IRRADIATION OF THE BRAIN

Dog No.	Time of Sacrifice. Days After Irradiation	Percentage of Water in Brains: Cerebral Gray Matter	Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
E23	1	79.3	65.6	79.9	79.8
E25	1	81.4	67.9	81.1	70.2
E20	2	77.0	64.4	78.2	70.0
E21	21	79.0	68.8	79.6	70.6
E22	21	77.4	64.2	78.5	69.3
E24	90	79.9	69.0	79.0	72.1
Averages		79.0	66.6	79.4	70.5

Under the conditions of our experiments, no increase in the water content of the brain resulted from intensive irradiation of the head. The unfavorable symptoms which undoubtedly sometimes follow roentgenotherapy may be due to changes in such factors as blood volume, cerebrospinal fluid balance or to actual hemorrhage (as suggested by Bailey, Sosman, and Van Dessel[25]).

The findings in the experiments here reported again demonstrate the remarkable stability of the water content of the dog's brain, both in corresponding specimens from a single animal (*e.g.*, cerebral and cerebellar gray matter) and from different animals under widely varying abnormal conditions.

For purposes of comparison, a composite tabulation of the average findings in these and previously reported groups of experiments is given in Table VII. Only the group subjected to high fever showed a consistent elevation in brain water content.

TABLE VII

COMPOSITE TABLE OF AVERAGES

Type of Experiment	No. of Experiments	Percentage of Water in Brains: Left Cerebral Gray Matter	Left Cerebral White Matter	Right Cerebral Gray Matter	Right Cerebral White Matter	Cerebellar Gray Matter	Brain Stem
1. Normal controls*	5	79.4	68.0			79.6	70.9
2. Trauma. No operation*	15	79.9	68.9			79.7	71.1
3. Left hemisphere exposed. No trauma*	7	79.0	68.6	79.5	68.5	79.9	70.9
4. Left hemisphere exposed. Trauma*	6	79.3	67.1	79.1	66.8	79.7	70.4
5. Bilateral nephrectomy	6	79.4	66.6			79.5	71.2
6. Bilateral ureteral ligation	5	78.3	66.1			79.3	70.6
7. Ligation of superior vena cava	4	80.0	68.2			79.7	71.7
8. Ligation of superior vena cava azygos vein	4	79.9	68.6			79.9	70.7
9. Hyperthermia	4	81.1	65.7			81.2	72.5
10. Irradiation	6	79.0	65.6			79.4	70.5

* Previously reported experiments.[1,2]

SUMMARY

The water content of various portions of the brain has been determined in dogs after bilateral nephrectomy, bilateral ureteral ligation, obstruction of the superior vena cava and azygos vein, severe fever and intensive irradiation of the head.

After high fever, a slight but consistent increase in the water content of the cerebral and cerebellar gray matter and of the brain stem was found. The water content of cerebral white matter was not significantly altered.

No significant alteration of the water content of the brain was found after the production of acute uremia, ligation of the superior vena cava and azygos veins, or intensive irradiation of the head.

REFERENCES

[1] Pilcher, C.: Experimental Cerebral Trauma. The Fluid Content of the Brain after Trauma to the Head. Arch. Surg., **35**, 512, 1937.

[2] Pilcher, C.: Experimental Cerebral Trauma. II. Further Observations on the Fluid Content of the Brain Following Trauma to the Head. Surg., Gynec., and Obstet. **72**, 755, 1941.

[3] Mason, M. F.; Resnik, H., Jr.; Minot, A. S.; Rainey, J.; Pilcher, C.; and Harrison, T. R.: Mechanism of Experimental Uremia. Arch. Int. Med., **60**, 312, 1937.

[4] Rees: Cited by Fishberg.[7]

[5] Traube: Gesammelte Beiträge, **2**, 551, 1870. Cited by Fishberg.[7]

[6] Volhard: Mohr and Stachelin's Handbuch der inneren Medizin. Berlin, **3**, 1342, 1918.

[7] Fishberg, A. M.: Hypertension and Nephritis. Philadelphia, Lea and Febiger, 1934.

[8] Blackfan, K. D.: Acute Nephritis in Children with Special Reference to the Treatment of Uremia. Bull. Johns Hopkins Hosp., **39**, 69, 1926.

[9] Blackfan, K. D., and McKhann, C. F.: Acute Glomerular Nephritis in Children. J.A.M.A., **97**, 1052, 1931.

[10] Blalock, A., Cunningham, R. S., and Robinson, C. S.: Experimental Production of Chylothorax by Occlusion of the Superior Vena Cava. ANNALS OF SURGERY, **104**, 359, 1936.

[11] Robinson, C. S., Cunningham, R. S., Blalock, A., Gray, M. E., and Rogers, B. C.: Chylous Effusions Produced by Experimental Ligation of the Superior Vena Cava Chemical and Cytologic Studies. Arch. Path., **24**, 303, 1937.

[12] Carlson, H. A.: Obstruction of the Superior Vena Cava: An Experimental Study. Arch. Surg., **29**, 669, 1934.

[13] Phillips, J.: Differential Diagnosis of Diseases of the Mediastinum. J.A.M.A., **78**, 1355, 1922.

[14] Lilienthal, H.: Thoracic Surgery. Philadelphia, W. B. Saunders Co., **1**, 260, 1925.

[15] Ehrlich, W., Ballon, H. C., and Graham, E. A.: Superior Vena Caval Obstruction with a Consideration of the Possible Relief of Symptoms by Mediastinal Decompression. Jour. Thorac. Surg., **3**, 352, 1933–1934.

[16] Waterfield, R. L.: Biot's Respiration in Superior Vena Cava Obstruction. Guy's Hosp. Rep., **78**, 305, 1928.

[17] Shapiro, P., and Jackson, H.: Swelling of the Brain in Cases of Injury to the Head. Arch. Surg., **38**, 443, 1939.

[18] McKenzie, P., and LeCount, E. R.: Heat Stroke. With a Second Study of Cerebral Edema. J.A.M.A., **71**, 260, 1918.

[19] Lichtenstein, L.: Pathologic Changes Following Therapeutic Hyperthermia. Am. Jour. Path., **15**, 363, 1939.

[20] Watts, F.: Report of Fifth Annual Fever Conference, Dayton, Ohio, 1935. Quoted by Wilbur, E. L., and Stevens, J. B.: Morbid Anatomic Changes Following Artificial Fever, with Report of Autopsies. South. Med. Jour., **30**, 286, 1937.

[21] Hartman, F. W.: Lesions of the Brain Following Fever Therapy. J.A.M.A., **109**, 2116, 1937.

[22] Schnabel, T. G., and Fetter, F.: Fever Therapy in Gonorrheal Arthritis and Chorea. Ann. Int. Med., **9**, 398, 1935.

[23] Chunn, G. D., and Kirkpatrick, C. L.: Fatal Result of Artificial Fever Therapy. Mil. Surg., **81**, 281, 1937.

[24] Hall, W. W., and Wakefield, E. G.: A Study of Experimental Heat Stroke. J.A.M.A., **89**, 177, 1927.

[25] Bailey, P., Sosman, M. C., and Van Dessel, A.: Roentgen Therapy of Gliomas of the Brain. Am. Jour. Roentgenol., **19**, 203, 1928.

[26] Alpers, B. J., and Pancoast, H. K.: The Effect of Irradiation on Normal and Neoplastic Brain Tissue. Am. Jour. Cancer, **17**, 7, 1933.

[27] Pendergrass, E. P., Hayman, J. M., Houser, K. M., and Rambo, V. C.: The Effect of Radium on the Normal Tissues of Brain and Spinal Cord of Dogs and Its Therapeutic Application. Am. Jour. Roentgenol., **9**, 553, 1922.

CEREBELLAR ABSCESSES OF OTITIC ORIGIN IN NINE CHILDREN

EIGHT RECOVERIES AFTER CANNULATION

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CEREBELLAR ABSCESSES in nine children have been treated surgically by the author during the past seven years. In each instance the symptoms of abscess became manifest after mastoiditis and mastoidectomy. Operative treatment was the same for all cases, and was delayed as long as possible without jeopardizing life from increased intracranial pressure, to allow the abscess wall to thicken and the acute symptoms of meningitis and cerebritis to subside. Slowing of pulse or respiration with increasing restlessness and stupor were the warning signs that surgical interference was imperative. No lumbar punctures were made, for fear of medullary herniation. Medication was avoided, especially with barbiturates or narcotic drugs which would produce added anoxic insult.

Under local anesthesia, a one-half inch trephine opening was made over the suspected cerebellar lobe with a Hudson bur, midway along a line between the occipital protuberance and the mastoid tip (Fig. 1). The dura was incised one-fourth inch to allow insertion of a blunt cannula with a side opening. The cannula was inserted into the abscess allowing its contents to escape. Usually, the first pus was thin and watery and the last thick and stringy. The abscess cavity was never washed out; the wound was always closed tight with silk.

Brief abstracts of each of the nine cases of cerebellar abscess in children are appended; certain details of the cases illustrate pertinent considerations in successful diagnosis, preoperative, surgical, and postoperative treatment of this condition.

ABBREVIATED CASE REPORTS

Case 1.—Judith S., age four, was admitted to hospital with painful swelling behind left ear; swelling had been discharging for two months. Child had been nervous, weak and without appetite since tonsillectomy a year before. Mastoidectomy was performed day following admission—a large quantity of pus was found and a small dural exposure was made. Extreme hyperemia of all structures made operation difficult but recovery was fairly uneventful until one month later, when child refused food, vomited, and temperature remained at 101° F. for a week. Spinal fluid showed 1,575 polymorphonuclear cells, with cocci in chains. Numerous spinal taps were made during the following month. Cultures were negative.

When first seen by the author, nine weeks after mastoidectomy, the child was listless, vomiting, and showed marked ataxia of the left arm. Optic disks were rosy. Seven days later the child became comatose, there was early papilledema and considerable ataxia of left arm and leg. At operation, resistance of abscess wall was felt at depth of 3 cm., and penetration with the cannula allowed green pus to extrude. Culture: *Streptococcus haemolyticus*. One ounce escaped before the child became livelier and the needle was

withdrawn to avoid traumatizing the cerebellum when the child moved. During a rapid postoperative recovery the child's papilledema disappeared within a week and the ataxia within a month. After five years of apparently normal health the child was again admitted to hospital with a stiff neck and high fever. Pneumococci were recovered from blood and spinal fluid and four days later patient expired from septicemia and meningitis.

Case 2.—Margaret L., age eight, was admitted to hospital, seven weeks after an opening of both eardrums, with painful and discharging ears. After a double mastoidectomy the child continued to be drowsy, with nausea, headache and weakness of left arm.

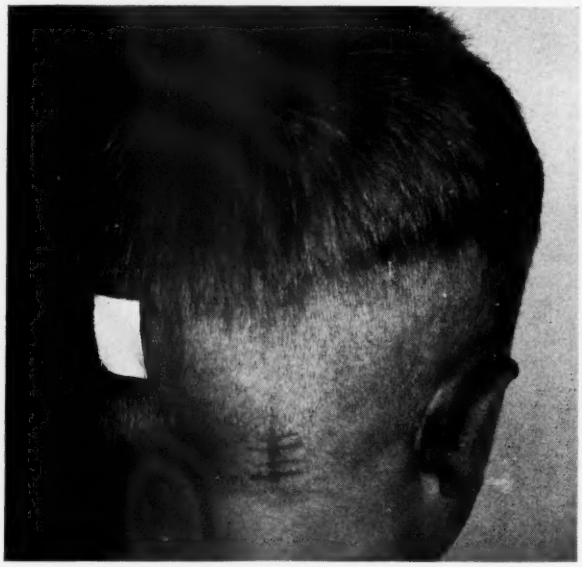

FIG. 1.—Billy H., Case 9: Showing recent scar over trephine opening. Patch of adhesive marks occipital protuberance.

Right mastoid region was reopened 12 days after mastoidectomy, the dura uncovered, and the right temporal lobe needled for a suspected abscess without obtaining pus. Several spinal punctures around this time showed 50 to 100 cells, mostly lymphocytes.

Patient was first seen by the author the day following reopening of right mastoid region. Child was semicomatose; pulse 60, temperature 99.6° F. Atonia and ataxia in left arm with early choking of optic disks. At operation upon the left cerebellar lobe, 45 cc. of thick greenish pus were allowed to escape from abscess whose wall was encountered at a depth of 3 cm. Pulse rose from 74, preoperatively, to 134, postoperatively, and child seemed improved. Culture: *Streptococcus haemolyticus.* After 11 days of stormy convalescence the child became unconscious, cyanotic, and pulse rate dropped to 60. Twenty-five cc. of glucose were administered, and patient immediately became conscious. After seven years this patient was getting along well in school and no neurologic abnormalities could be found.

Case 3.—Harry C., age five, was readmitted to hospital, 15 days after a left mastoidectomy, with complaint of vomiting and headache, but did not appear acutely ill. Pulse 100; temperature normal; R.B.C., 3,150,000; W.B.C., 17,200. Spinal tap revealed clear fluid under increased pressure, with 76 cells. Culture: Staphylococcus. Following spinal tap, the child complained of neck pain, its head was retracted and its condition became rapidly worse.

Seen by author on following day, the child was drowsy but cooperative, his pulse varied around 60, the fundi showed early choking of the disks, and there were marked

ataxia and atonia of the left arm. The neck was not rigid but the head was thrown back because of pain several times during examination (cerebellar fits). At operation, cannula was introduced directly into cerebellar lobe to a depth of 6 cm. without encountering resistance. Cannula was introduced slightly upward without meeting abnormal resistance, but when introduced slightly downward encountered resistance at a depth of 5 cm. On withdrawing slightly, about 2 to 3 cc. of thin, flaky pus escaped.

FIG. 2.—Left to right: Margaret L., Adelore W., Bruce R., Gloria D., Mary R., Sally L., standing on the foot on the same side as the cannulated cerebellar abscess.

The condition of the patient seemed to be somewhat improved postoperatively, but the child continued to throw its head back because of pain. On the second postoperative day breathing suddenly stopped following a spell of extreme restlessness and death followed shortly afterward.

Case 4.—Adelore W., age 11. At age five patient underwent bilateral mastoidectomy following a three months' fever following scarlet fever. Admitted to hospital six years later with vomiting, severe headache and photophobia. Neck rigid. Temperature, 100.6° F. During secondary right mastoidectomy, dura and sinus were exposed and appeared healthy. A right facial paralysis was noted on reaction from anesthesia, and after operation temperature became normal, but the boy was increasingly drowsy and a right rectus palsy developed. Optic disks were elevated 2 to 3 diopters.

First seen by the author 12 days after secondary mastoidectomy, the boy was alert and cooperative but his speech was slurred. Paralysis of right sixth and seventh nerves was noted. There were marked atonia and ataxia in the right arm. Bilateral papilledema, 3 diopters. W.B.C., 16,250, 76 per cent polymorphonuclears. Temperature, 98.6° F. Pulse, 70. At operation, cannula inserted into center of right cerebellar lobe encountered pus at depth of 2 cm. Cannula removed after 20 cc. of pus had been extruded. Culture: *Streptococcus haemolyticus.* Recovery was uneventful except for a persistent slight right facial weakness, and four years later child was apparently in perfect health.

Case 5.—Bruce R., age ten. After several years in which patient was troubled with right earache with discharge in the wintertime, he was admitted to hospital with headache, earache and discharging right ear. Culture: *Streptococcus haemolyticus.* Child was discharged from hospital one week after right mastoidectomy and recovery

seemed normal for three weeks, after which the boy complained of headache and ran a spiking temperature. Blood culture showed no growth. W.B.C., 22,800; polymorphonuclears, 84 per cent. Four weeks after the mastoidectomy another mastoidectomy was performed on the same side. Temperature became normal but drowsiness increased, accompanied by headache.

When first seen by the author the boy was lethargic but cooperative, complaining of frontal headache. The neck was not rigid. There was no papilledema, although the optic disks were rosy. Coarse nystagmus on looking to the left, with the slow component to the right. Transient right facial weakness, especially noted on smiling. Ataxia on the right in the finger-to-nose and finger-to-finger tests. Atonia of the right arm. No abnormality noted in the deep and superficial reflexes. W.B.C., 14,500; polymorphonuclears, 95 per cent. At operation, cannula encountered resistance as of tentorium at a depth of 3 cm. Cannula reinserted slightly downward and toward mastoid tip, striking no resistance but obtaining pus at a depth of 4 cm. Ten cc. of thick greenish-yellow pus allowed to extrude itself. On inserting the instrument 1 cm. farther, a resistance was felt as of the bottom of the abscess cavity. When no more pus escaped, the cannula was withdrawn. Culture: *Streptococcus haemolyticus.*

There was immediate improvement in the headache, but the boy continued to be drowsy. After three weeks the wound was opened and about 5 cc. of pus found outside the dura. Following this the patient made a progressive and uneventful recovery. Three years after operation neurologic examination was entirely normal, the boy was getting good grades in school, was active in athletics and had no complaints of any kind.

Case 6.—Gloria D., age six, was admitted to hospital with pain and swelling behind right ear after complaining for two months of recurring earache on right side. Right mastoidectomy revealed considerable pus. Culture: *Streptococcus haemolyticus.* Convalescence was uneventful, but a month later the child was readmitted to hospital after ten days of headaches and fever. Child was listless, uncooperative, and weakness of right arm was noted. Papilledema, 6 diopters. Secondary mastoidectomy with needling of right temporal lobe did not reveal pus. Sulfanilamide was given but discontinued because of increasing stupor.

When first seen by the author the girl was semiconscious but cooperated enough to raise her arms. The right arm was ataxic and could not be supported voluntarily because of atonia. The grip was fair in both hands. Moderate neck rigidity. Diminished knee jerks. Marked choking of disks. W.B.C., 12,500. Temperature, 98.6° F. Pulse, 65. At operation, definite resistance was found at a depth of 2 cm. On pushing the cannula through this resistant tissue, yellow pus was encountered and one ounce drained. When no more pus would flow, the cannula was withdrawn. The tension on the dura was markedly decreased following this procedure. On discharge two weeks after operation, there was no evidence of atonia or ataxia, although a decreasing papilledema was still present. When last seen, two years after operation, the neurologic examination was entirely negative. The child was doing well at her studies and was said to be an excellent tap dancer.

Case 7.—Mary R., age seven, was admitted to hospital after six days of pain and discharge from right ear. Temperature, 101.5° F. During mastoidectomy 11 days later, pus under pressure was found. Culture: *Streptococcus haemolyticus.* Temperature dropped to normal following operation but child became drowsy and vomited.

Patient was first seen by the author ten days after mastoidectomy. Right arm was ataxic. Photophobia was noted but optic disks appeared normal. At operation, abscess cavity was entered at depth of 3 cm. and 10 cc. of thin pus escaped. Aspiration with a 20 cc. syringe produced 5 cc. of thick, slimy pus before needle clogged and was withdrawn. Culture: *Streptococcus haemolyticus.* Patient improved but remained irritable, vomited occasionally and showed ataxia of right arm and nystagmus. Fundi remained normal and mastoid wound healed completely.

Three months later child was again admitted to hospital because of increasing head-

ache, vomiting and atonia of right arm and leg. Examination showed bilateral choked disks of 3 to 4 diopters, right rectus palsy. The child appeared to be myxedematous. Extreme ataxia and atonia in the right arm and leg. During secondary operation very marked resistance was encountered at a depth of 5 cm. with the cannula directed toward the left pupil. This was at first thought to be tentorium, but on pushing the instrument further a cavity was entered and two ounces of thick greenish-yellow pus escaped. When dropping of the pus through the cannula slowed up, aspiration with a syringe was attempted, but without obtaining more pus. Culture: *Streptococcus haemolyticus.*

This child was discharged six days after operation. The irritability disappeared immediately. One month after operation the myxedematous appearance had disappeared, the optic disks were flat and only a trace of ataxia and internal strabismus remained. A year later no neurologic abnormalities could be noted and the child was getting along well in school.

Case 8.—Sally L., age five, was admitted to hospital with left-side earache, vomiting and temperature of 100° F. History of bilateral headaches for over three years. The ear had been opened the day before admission and sulfanilamide was given for four days after admission. Roentgenograms showed second degree left mastoid involvement and complete left mastoidectomy was performed ten days after admission. Culture: *Streptococcus haemolyticus.* Temperature continued to range from 99° to 102° F., and the girl became increasingly irritable and irrational. She was drowsy but presented no abnormal neurologic signs except neck rigidity. Spinal fluid examination showed no increase in pressure; 285 polymorphonuclears; Pandy, four plus. Spinal fluid culture, staphylococcus, atypical. Sulfanilamide was again administered and several transfusions given. Although the temperature became normal, the child grew increasingly drowsy with generalized twitchings, suggesting a tuberculous meningitis to one observer.

When first seen by the author, three weeks after mastoidectomy, she was drowsy and irritable. Early papilledema was noted and the neck was rigid. There was marked ataxia and atonia of the left arm and leg when raised by examiner, the child being entirely uncooperative. Because of the irregular pulse, ranging from 42 to 60, and the desperate appearance of the child, operation for suspected cerebellar abscess was performed immediately. On incising the dura a small amount of cerebellar cortex herniated through the small nick. A cannula was inserted and penetrated the resisting abscess wall at a depth of 2 cm. One-half ounce of yellow fluid squirted out and gentle aspiration removed another one-half ounce of thick yellow pus. Culture: *Streptococcus haemolyticus.*

During the procedure the child became more rational and cooperative. Recovery was immediate and the patient was discharged five days after operation. A year later neurologic examination was entirely negative and the parents thought the child normal in every way.

Case 9.—Billy H., age four. Headache, irritability and neck rigidity had been present before a right mastoidectomy. After operation the child became drowsy and developed increasing ataxia of the right arm and leg. There was little elevation of temperature at any time.

Two weeks after mastoidectomy the patient was seen by the author and a cannula was introduced into the right cerebellar lobe allowing 45 cc. of pus, under marked pressure, to escape. Culture: *Streptococcus haemolyticus.* Recovery was uneventful and neurologic examination seven months after operation was entirely normal (Fig. 2).

Discussion.—In all the cases the principal diagnostic and localizing signs were atonia and ataxia of the arm on the same side as the abscess. These signs could be observed, whether the child was cooperative, irritable or stuporous, if the arms were lifted from the bed and allowed to fall away. In addition, various symptoms of cerebral anoxia from increased intracranial pressure were found: character change, headache, irritability, vomiting, papil-

ledema and stupor. Occasionally, differential diagnosis was difficult between a brain abscess in the cerebellar lobe on the side of the atonic and ataxic extremity and in the temporal lobe on the opposite side. With the cerebellar abscess the grip in the ataxic extremity is little different from that in the other hand. With the temporal abscess, the arm is usually paretic and the grip is weaker in the hand on the side opposite the abscess.

In waiting for a cerebellar abscess to wall off, there is a perilous balance between brain infection, on the one hand, and increased intracranial pressure, on the other. Chance, as well as judgment, may play a great part in the successful outcome of any case. The value of surgery is principally in the mechanical relief of pressure, giving the brain a better chance of conquering and surviving its infection.

After the upper attachment of the suboccipital muscles is spread with a self-retaining mastoid retractor, the trephine opening is ordinarily made about one-half inch below the transverse sinus. Care must be taken that the opening is not over or above the sinus. After nicking the dura, the cannula is gently forced into the cerebellum and directed slightly toward the mastoid tip. In only one case was the abscess found to be more centrally located. The cannula should be inserted and withdrawn very slowly to allow thick pus to escape. Pressure from within is usually sufficient to empty an abscess completely because, when the pus stops dripping through the cannula, aspiration with a 20 cc. syringe seldom obtains more pus. Still, it is well to use the syringe to make sure the cannula has not been plugged with fibrinous material. No irrigation of the abscess cavity is employed.

Any anoxic insult which might be added incident to treatment must be avoided. Operation should be performed under local anesthesia and narcotic or hypnotic drugs are contraindicated. In all of the cases outlined chemotherapy was discontinued as soon as the cerebritic stage was passed and before any surgical intervention was attempted.

Previous attempts had been made in two of the cases to needle a suspected temporal abscess through an infected mastoid wound. Such a practice proves the considerable immunity of the brain to infection, but is not a desirable neurosurgical procedure. Spinal puncture should not be made if a cerebellar abscess is suspected, for this procedure increases the danger of medullary herniation.

The only child in the series which died after operation was fighting not only an active staphylococcic meningitis, but also the untoward effects of a spinal tap, which made immediate operation imperative and prevented proper walling-off of the abscess. The other child, who died of pneumococcic meningitis after five years of good health following the drainage of a streptococcic abscess, is just another illustration of the variable immunity of the central nervous system to different types of organisms.

Grateful acknowledgment is made to Drs. William S. Gonne, J. Milton Robb, G. M. Laning, Seymour Ross, William G. G. Coulter, J. Gerard Campbell, Carl C. McClelland, Wesley W. Wilson, and Jacob S. Wendel, who referred these cases to the author.

THE SURGICAL TREATMENT OF INTRACRANIAL ANEURYSMS OF THE INTERNAL CAROTID ARTERY*

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INTRACRANIAL ANEURYSMS arise on any part of the arterial vascular tree. Over one-half spring from the circle of Willis, the remaining are distributed throughout the brain and from the vertebral and basilar arteries. There are three types of intracranial aneurysms: (1) Congenital, comprising about 80 per cent of the entire number; (2) arteriosclerotic (about 15 per cent); and (3) mycotic (about 5 per cent). Contrary to a very prevalent opinion, syphilis plays no rôle, or almost none, in the formation of these aneurysms. There are no surgical possibilities in the mycotic aneurysms, which are one of the terminal phases of endocarditis, and are almost always in the brain substance and on the middle cerebral artery or one of its branches. Arteriosclerotic aneurysms offer very little returns from surgery; as yet none have been cured, though it is quite probable that the vertebral and basilar aneurysms may be benefited by ligation of one vertebral artery in the neck. It is principally with the congenital aneurysms that surgery has a place in treatment. Usually they are small berry-like nubbins in one of the vascular trunks—not uncommonly they are multiple. Since their walls are congenitally defective, they give rise to intracranial hemorrhage—usually the so-called subarachnoid hemorrhage—and in the early years of life, although they may rupture in later life.

Until a sudden rupture, aneurysms are usually silent. The immediate result of the hemorrhage depends in large degree upon the presence or absence of opposing tissue at the site of the rupture. If the rupture is into cerebral substance, the bleeding may be controlled, and a large progressive false aneurysmal sac will form and in time, by gradual expansion, give signs and symptoms like those of a brain tumor. Should the rupture be along a structure like the third nerve or the carotid artery itself, the bleeding may be controlled temporarily, but subsequent ruptures will probably occur and usually end fatally. Should there be no opposing tissue, the bleeding would then be into the cerebrospinal fluid (the cisternae) and rapid, fatal hemorrhage is almost inevitable.

The great deterrent to operative intervention in subarachnoid hemorrhage is the inability to localize the aneurysm by symptoms or signs. At times, there are prodromal manifestations but all too frequently the patient passes quickly into coma and then, all too frequently, there are no objective localizing signs.

* Read before the American Surgical Association, White Sulphur Springs, W. Va., April 28, 29, 30, 1941.

If it were even possible to localize the side (right or left) of the aneurysm, the operative exposure would be adequate to disclose the aneurysm, if it were located on the circle of Willis. This is a hope for the future, for up to the present time the only aneurysms that have been operated upon successfully are those causing a third nerve palsy or paralysis—a sign that is almost but not quite pathognomonic of an aneurysm and its location.

In a search for better and earlier means of diagnosis of aneurysms and their location, I have analyzed 103 cases that have appeared in the records of the Johns Hopkins Hospital. In a very high percentage of cases, no help was elicited, but in many of them there was adequate information to determine the side of the lesion. In nearly all of the aneurysms of the middle cerebral artery there was hemiplegia, but it is highly improbable that more than an occasional aneurysm of this vessel can ever be cured without a permanent hemiplegia, and treatment of this character would not be considered. On the other hand, some aneurysms of the anterior cerebral artery give a partial hemiplegia or Babinski, and these are amenable to treatment, although none have as yet been cured. Bilateral cerebellar and brain-stem signs of sudden onset may also indicate aneurysms of the basilar and vertebral arteries, but here again there are little prospects of a cure by surgical means, at least none have yet been successfully treated. It is the silent aneurysms, with few or no signs or symptoms arising from the internal carotid arteries and the circle of Willis, that offer the maximum from prompt surgical treatment.

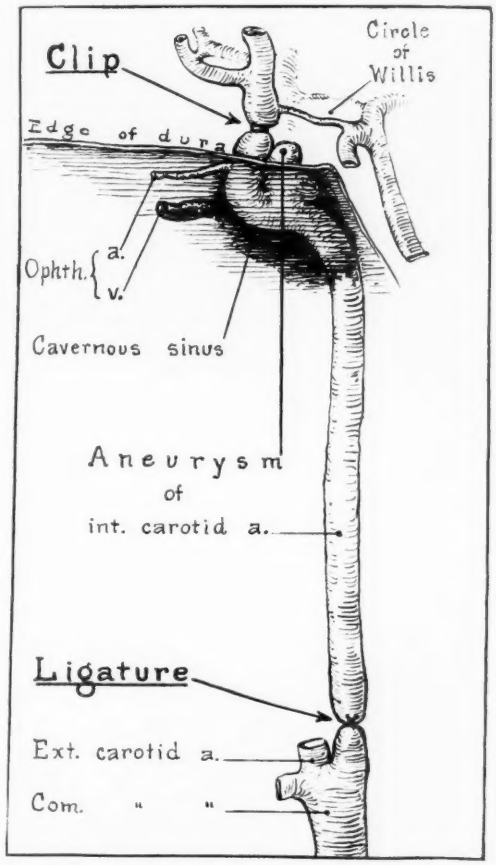

FIG. 1.—Diagrammatic drawing illustrating the method of curing carotid aneurysms arising within the carotid canal. A clip is placed on the internal carotid artery intracranially, and the internal carotid artery is ligated in the neck. This traps the aneurysm between the two ligatures, and the only sizeable branch between the ligature is the ophthalmic artery. Vision is not lost as the result of the ligation.

The only symptom that is useful in detecting the side of the aneurysm is an unilateral headache, or pain in one eye. This may or may not be present, either as a prodromal symptom before rupture, or as an excruciating pain at the time of rupture; and even occasionally it may be misleading. A positive

Babinski sign may at times betray the side of the lesion; but by far the most important sign of all is weakness of a third nerve.

Intra-arterial injections of thorotrast have for some time been used to define aneurysms and with remarkable results. Against its use is the risk of cerebral emboli, the frequent necessity of injecting both internal carotid arteries, since only one side fills well with one injection; and in the acute stage of bleeding the patient is much too ill. For patients who are not in the acute stage of subarachnoid bleeding, it will doubtless be a distinct asset, but should be employed with caution and discrimination.

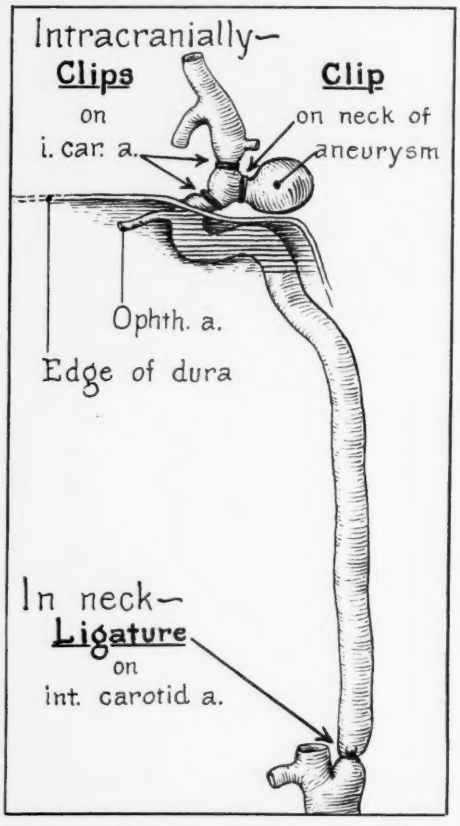

FIG. 2.—Diagrammatic drawing illustrating the method of treating intracranial aneurysms arising from the internal carotid artery, before the first branch is given off. The neck of the aneurysm may be clipped and nothing done to the internal carotid, or the internal carotid may be clipped on either side of the neck of the aneurysm, thus isolating it. The aneurysm is then shrunk by the electrocautery, in order to remove its contact with the third nerve, or it may actually be removed; this was done in one case.

Thirteen intracranial aneurysms of the internal carotid artery have been operated upon; all have been diagnosed and localized by a third nerve palsy or paralysis, plus sharp, severe, sudden pains in the eye and the corresponding side of the head. Six of these arose in the carotid canal and broke through into the cranial chamber alongside the internal carotid artery. Five of these are cured, the longest for four and one-half years. The single death was due to a rupture of the carotid artery in applying to a very large arteriosclerotic vessel a silver clip that was too small. This was a case of an arteriovenous aneurysm (pulsating exophthalmos). The arterial aneurysm which had ruptured and caused this arteriovenous fistula was found at necropsy. Seven arose from the internal carotid artery intracranially, before the anterior cerebral artery is given off. Five of these are cured and two have died.

Two of the five cures were obtained by placing a silver clip on the neck of the aneurysm, leaving the carotid artery intact. The remaining three cures were obtained by clipping or coagulating with the cautery the internal carotid artery on both sides of the aneurysm. The two deaths were due to (1) an abnormally placed posterior communicating artery, which was between the two clips and prevented collateral circulation; and (2) to subsequent rupture of the electrically coagulated internal carotid artery. This

occurred one month postoperative, after the patient had returned home, and was presumably cured. Ligation of the internal carotid artery in the neck would have prevented this death.

The mortality in this series is, therefore, 23 per cent—the cures 77 per cent.

DISCUSSION.—DR. FRANCIS C. GRANT (Philadelphia, Pa.): This question of aneurysms and their treatment is a matter of considerable interest because I think we may find that a good many of the cases that we see which have been classified as subarachnoid hemorrhage are going to turn out to be aneurysms, and may offer post-operative treatment.

The case that Doctor Dandy referred to, that was operated upon by him, in which the diagnosis of aneurysm was made by the use of thorotrast, has, in our instance at least, opened a good many possibilities. We have had two similar cases since, in which the thorotrast has been used and the aneurysm identified, and we are hoping to have the opportunity to operate upon those particular cases.

Our experience with aneurysm has not been as fortunate, so far as the operative procedure is concerned, as Doctor Dandy's has been.

During the last ten years, we have had 14 cases of aneurysm that have gone through the clinic and been identified, nine of them clinically and five pathologically. The five pathologic cases have been found in a series of, roughly, 1,100 verified brain tumors, so I presume the percentage of aneurysm to all other cases is about one-half of 1 per cent. The cases that are considered as having been verified clinically are cases similar to the ones to which Doctor Dandy referred, where there has been a paralysis of the various optical nerves, usually with hemiplegia; and on the history; and, at times, by roentgenologic and other evidence, the case has been suggestive of aneurysm, but unfortunately we have not, as I say, realized the operative possibilities in those cases which have been sent home.

The type of case that we have seen most commonly is similar to one that we had two years ago, with aneurysm of the basilar artery; a presumptive diagnosis was made of a cerebellar lesion. The patient died rather suddenly, after the administration of an enema. This lesion was found.

The other kind has been of the type where there has been a large intracerebral aneurysm; the possibilities as far as operation is concerned in those cases, of course, being very limited. But I am quite sure that most of these cases of subarachnoid hemorrhage—certainly those that show clinical and pathologic evidence of the involvement of the ocular nerves, particularly the third—should be subjected to thorotrast injection. With the injection of thorotrast, one may very well find the position of the aneurysm. As Doctor Dandy has said, if it lies on the circle of Willis, very little can be done, but if it lies along the carotid, certainly, exposure is warranted and an attempt can be made either to trap the aneurysm between the silver clips, as he suggested, or to put a silver clip on the neck of the aneurysmal sac itself; and by that means I see no particular reason why a good many of these cases should not be cured. Of course, it is not quite as easy an operative procedure as one might gather from Doctor Dandy's description, but, nevertheless, it is an operative procedure which, to my mind at least, is entirely justified, because if nothing is done these aneurysms will go on to rupture, with ultimate death of the patient.

DR. GILBERT HORRAX (Boston, Mass.): This is a most important communication of Doctor Dandy's, and I am sure it interests all of us, but particularly the neurosurgeons. It has opened up a line of treatment for certain types of intracranial aneurysms, which I am sure we must all follow in the future.

We have not been fortunate enough to identify an aneurysm intracranially which we could clip or trap in the way Doctor Dandy has described. However, we have had six examples of intracranial aneurysms which we have exposed at operation and have treated in another way, a way which has been described by Mr. Jefferson, of Manchester, England, and by Mr. Dott, of Edinburgh. This method consists in packing pieces of muscle around the aneurysm and thus hope at least to prevent any further rupture. These

patients have all survived and are alive anywhere up to five or six years at the present time.

One aneurysm, upon which we have not operated, was demonstrated by thorotrast, and one was identified but nothing was done to it since nothing could be accomplished, except to divide the ninth nerve, because of the pain the patient was having.

It seems to me we must be a little conservative about the attitude we take in regard to operation upon aneurysms, as there have been a large number of patients passing through the clinic who have had the diagnosis of intracranial aneurysm made, because of third nerve palsy and pain over the eye of the same side. Whether they are aneurysms or not, we do not know because we have not subjected them all to thorotrast. In fact, we have only, in two instances, demonstrated the presence of aneurysm by thorotrast. The other cases have not, as a rule, shown anything roentgenologically from which a positive diagnosis could be made, so the aneurysm diagnoses have been made on symptomatology and signs, but a large number of cases with one rupture have recovered and gone on for many years in perfectly good health. Thus, it seems to me there is a chance for a good many of these aneurysms to take care of themselves, if they have only a single rupture, because very possibly when there has been subarachnoid bleeding around them a clot is formed, and, because of the organization of that clot, I believe some of the aneurysms permanently cure themselves.

It is a most interesting and valuable paper. I think we should be on the watch for those aneurysms which we can cure in this way by ligation. But if the aneurysm, as presented at operation, does not offer a chance of putting a silver clip on it, this method of putting the muscle around it, I think, is an excellent one.

CANCER OF THE LIP*

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PART II

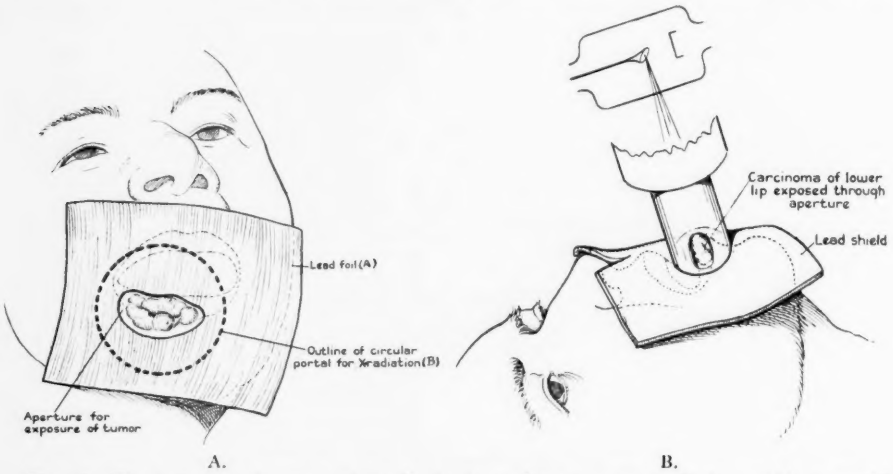
Radiation Treatment of the Primary Lesion.—Superficial cancers of the lip (1–5 Mm. in thickness), whether small or covering an area of several square centimeters, are preferably treated by radiation, in our opinion, not because of a higher cure rate but because of the superiority of the cosmetic results. For lesions of greater thickness, the choice of radiation or surgery is somewhat optional and depends upon the available equipment and the skill and experience of the surgeon in the use of one or the other of these methods.

For early growths, which have not progressed much farther than keratoses, unfiltered radon is an excellent method. At Memorial Hospital such radiation is obtained by the so-called "radon bulb" which consists of a thin glass bulb about 5 Mm. in diameter containing 200–500 mc. of radon seeds which is held in contact with the lesion by a special holder for a few seconds or minutes, depending on the desired dose. There is no filter except the thin wall of the glass bulb. With doses of from 400 to 1,000 mc. minutes (depending on the extent of the lesion), these small growths can be controlled with a minimum of discomfort and with a nearly perfect cosmetic result. This method should not be employed in lesions of greater depth than about 1 Mm. In many of these early growths a biopsy is not justified, and if no histologic proof of cancer is obtained, the cases cannot be included in a statistical report of cures of cancer of the lip—an objection of academic rather than of practical importance.

For superficial lesions, more advanced than the above but whose thickness is not greater than 2–3 Mm., there are several effective radiation methods; namely, (1) low voltage (100–140 K.V.) lightly filtered roentgen radiation; (2) contact application of filtered radon tubes held in dental compound moulages; (3) interstitial radiation in the form of gold radon seeds, radon, or radium needles. Although all of these methods employed singly are efficacious, the best cosmetic results are undoubtedly obtained by low voltage roentgen radiation supplemented in some instances of thicker lesions by the implantation of small doses of interstitial radon.

In using low voltage roentgen radiation, the surface of the tumor in the lip (including an apparently healthy margin of 3–5 Mm.) is exposed through

an opening in a shield of lead foil applied to the lip (Fig. 6). Individually fitted shields should be made for each case, and the lesion itself so positioned that the surface of the tumor may be exposed as nearly as possible at an angle of 90° to the incident beam. If the growth tends to extend on to the inner surface, a moulage of dental compound in the lower gingivolabial gutter may be used to evert the lip, so as to expose the entire growth. The dosage must vary considerably, depending on the diameter of the area exposed and the quality of the roentgen radiation, as determined by the voltage and the


Lead foil(A)
Outline of circular portal for X-radiation(B)
Aperture for exposure of tumor
Carcinoma of lower lip exposed through aperture
Lead shield

A. B.

FIG. 6.—The treatment of cancer of the lip by low voltage roentgen radiation. (A) A special shield of lead foil is used with an aperture which is large enough to expose the tumor and a margin of 3–5 Mm. (B) The cone which limits the beam of the roentgen rays is then carefully centered over this aperture.

filter. It has been found, in our clinic, that in such superficial roentgenotherapy, the necessary dosage as expressed in r may be made to vary more than 100 per cent by changing one or more factors as, for instance, by dropping the voltage from 140 to 100 K.V., by varying the filter from 1–3 Mm. Al, or by dividing the treatment into fractions over a period of five to 15 days instead of giving the entire exposure at one sitting. Since there are so many variable factors, it is difficult to give complete or specific dose recommendations for this type of therapy. In general, for areas about 1 cm. in diameter, the required dosage ranges from 9,000–15,000 r, depending upon the exact physical factors of the roentgen ray machine, and whether the irradiation is administered all at one time or in fractions over longer periods (five to 15 days). In lesions of 4–5 Mm. thickness, the advisability of supplementary irradiation by a small dose of radon seeds inserted under the base of the growth should always be considered. The individual strengths of the radon seeds for such supplementary treatment should not exceed 1–1.5 mc. each. Not more than two or three seeds should be used in the average case, and they should always be placed at a depth of at least 5 Mm. below the surface of the vermilion border so as to minimize the danger of surface necrosis.

Contact irradiation by filtered radon tubes is also an excellent method, although it has the disadvantage of producing more late radiation sclerosis and atrophy than soft roentgen radiation. In recent years, this method has

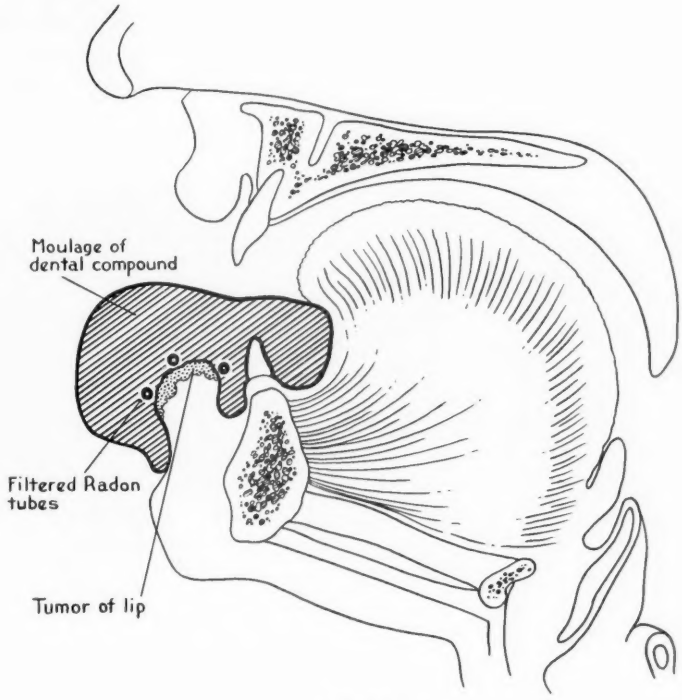


FIG. 7A.

FIG. 7B.

FIG. 7.—A and B: Dental compound moulage to hold filtered radon in contact with lower lip for treatment of superficial lesions.

been replaced almost entirely at the Memorial Hospital by low voltage roentgen radiation for lip cancer. In the technic of contact irradiation devised by Janeway,[26] the filtered radon tubes are held in contact with the lower lip in a moulage of dental compound (Fig. 7 A) which is made as follows: About one and one-half squares of ordinary dental modeling compound are heated to a soft plastic consistency and molded about the lower lip. Some of the compound is forced down into the gingivolabial gutter and also between the teeth, in such a manner as to hold the lip, the growth, and the radiating sources away from the lower alveolar ridge. The patient is instructed to bite into, *but not through*, the portion of the compound which has been forced between the teeth. While the compound is still warm and plastic, it is carefully molded about the lip and the growth so as to cause a minimum distortion of these parts (Fig. 7 B). If the patient is seated in front of a wash bowl and a rubber tube is connected with the cold water faucet, the moulage may be rapidly cooled and hardened before removal.

The moulage, when removed, should present an accurate impression of the lower lip and a visible imprint of the lesion. There should be a ridge of the compound 6–7 Mm. thick between the inner surface of the lip and the alveolar ridge, and, also, the undistorted imprints of the teeth, so that the applicator can be replaced exactly in its original position. If the patient wears dental plates, these are left in place when the impression is taken. The plates will come out embedded in the mold when the latter is removed and will serve, as well as the natural teeth, to hold the applicator in its correct position.

When the moulage is removed, the portion which represents the lower lip should show a definite imprint of the lesion. Holding the moulage next to the patient's lip, and guided by inspection of the growth, an outline is scratched (or otherwise marked) so as to encircle the imprint of the lesion by a margin of at least 5–6 Mm. The applicator is then ready for the placement of the radon tubes. The platinum radon tubes, as used in our clinic, are 1.6 cm. in length with a wall thickness of 0.5 Mm. of platinum, and they contain glass tubes of radon. Their individual strengths may vary from 25 to 75 mc. each. If a number of short radium element needles are available, they may be substituted for the radon tubes just described. With a hot metal die of the same size as the radon tubes, grooves are made within the outlined area so that the tubes, when placed, will lie from 4–6 Mm. apart and about 1–2 Mm. below the surface of the mold. Their position is so arranged that they are distributed as evenly as possible over the surface of the lesion to produce a maximum of cross-firing. The tubes are sealed in place by melted paraffin. The area to be irradiated (that inscribed by the scratch mark surrounding the lesion) is then calculated in square centimeters.

The applicator is now ready for use. It is carefully replaced exactly in the position in which it was made, care being taken that the teeth or gums fit accurately into their original positions. The patient is instructed to force his lower lip up firmly into the groove into contact with the radon tubes.

In order to protect the upper lip from unnecessary radiation, a small piece of lead may be placed between it and the upper surface of the moulage, or a roll of gauze will hold the upper lip away and protect it by distance.

The dosage is calculated in millicurie hours per square centimeter of area treated, and it should be emphasized at this point that the figures given below are correct only for the filter specified, that is 0.5 Mm. of platinum. If the area is small (up to about 3 sq. cm.), a dose of about 85–90 mc. hrs. per sq. cm. is given. The minimum total dose ever given with this applicator should be at least 240 mc. hrs. with three tubes. Moderately thicker lesions should receive higher doses per square centimeter. If the area to be treated is 5–6 sq. cm. or more, the dose should be decreased to 70–80 mc. hrs. per sq. cm. (350–500 mc. hrs. total), because of the cross-firing from the several tubes. In any case, it is best to err moderately on the side of heavy rather than light dosage, since delayed healing is preferable to recurrence. As with unfiltered roentgen radiation, lesions over 4–5 Mm. in thickness should, ordinarily, have supplementary interstitial radon in the form of one or more weak gold seeds implanted under the base of the lesion. The interstitial use of radon seeds or radium needles alone, as advocated by some authors, is not suitable for lip cancer because of the high incidence of radionecrosis if the doses are adequate.

Operation may be refused in certain cases of bulky tumors of the lip which, as a general rule, are best treated by surgery. If the patient will not submit to surgery, radiation is the only other possible method of treatment, and adequate dosage necessitates the use of interstitial irradiation with seeds or needles at least as a supplement to external irradiation. The dosage in such cases must be calculated in the same manner as for bulky tumors elsewhere, with a tissue dose of 8–10 S.E.D. (skin erythema doses) given into the tumor. The method of calculating tissue doses of radon seeds for tumors of various sizes is given in Table II. Although the treatment of these bulky lesions of the lip with massive doses of interstitial radiation in the form of seeds or needles is invariably complicated by a rather long period of healing, excellent results are often obtained.

Surgical Treatment of the Primary Lesion.—Although from the cosmetic standpoint radiation methods are almost always superior to surgical excision for small lesions of the lip, it must be admitted that the wedge-shaped excision for small tumors will offer an equally good chance of cure *provided that a safe margin is allowed.* Except in the determination of this safe margin (5–7 Mm.), these operations are not difficult, and in some surgical clinics are performed in the Out-Patient Department. No particular description of technic will be attempted in this report except to state that the careful approximation by sutures of both the skin and mucous membrane edges is essential for the best cosmetic results.

Cheiloplasty.—In the more advanced, deeply infiltrating and eroding lesions 2 cm. or more in diameter (which make up over one-third of our total group), surgical excision and plastic closure is undoubtedly the preferable

method. In such cases, the simple V-shaped excision is usually inadequate. To be safe, the margin of the excision in these lesions must be wider (1 cm. or more) than in early cases; the operative defects are, therefore, rather extensive, and the closure complicated. The details of the technic of plastic repair of these operative defects are of considerable importance in obtaining the best cosmetic and functional results.

These advanced lesions are often 5–6 cm. in diameter, or even larger, and may invade the entire vertical diameter of the lip and extend into the skin and subcutaneous tissue over the chin or laterally past the labial commissures into the substance of the cheeks or upper lip. In other cases, the growths may fungate from the surface so as to form bulky tumors without much infiltration, of such weight as to produce marked ectropion of the lower lip. These bulky noninfiltrating and fungating tumors are usually not of the most malignant variety and are commonly found without evidence of cervical metastases even after two to three years' duration. From the standpoint of cure, the large size of a lesion is less important than the presence of metastases or invasion by the primary lesion of the gingivolabial gutters and jaws. Provided that the primary growth can be removed with a safe margin of normal tissue, even the largest defects can be repaired by some form of plastic procedure, either primary or delayed. Even though the operative defect may be difficult to close, there should be no compromise to the removal of a safely wide margin of normal tissue.

There is probably no single type of operation for which more allegedly different technics have been described. As far back as 1859, von Bruns[61] had reviewed the literature, and classified 32 operations by 52 authors, and several times that number have been subsequently published. Most of these are merely repetitions of the older technics with slight modifications, although the later authors often claim credit for their invention. From the standpoint of pure mechanics, a study of this material will reveal that many of the technics are highly impractical or unnecessarily complicated. We believe that the whole subject can be reduced to a few essential principles which permit of an almost infinite number of modifications; these principles are: (a) The use of sliding lateral cheek flaps based upon the principles of Burow[51] and Bernard[3]; (b) pedicle flaps brought down from the upper (or opposite) lip (Estlander[19]); and (c) tubed pedicle-flaps brought from the neck or anterior chest wall, as introduced by Filatoff.[21] The detailed basic technic for such operations has already been published by one of us.[37] A number of the most useful procedures for this purpose are shown diagrammatically in Figures 8 and 9. As previously mentioned,[16, 20, 22, 42, 59] the possible variations are almost infinite in number, and it is perfectly natural that the individual surgeon should introduce his own, provided that he makes no undue claims to originality.

The most satisfactory anesthetic for these operations is conduction anesthesia by novocain injection of the third divisions of the fifth cranial and of both infra-orbital nerves. For the incisions which extend below the lower

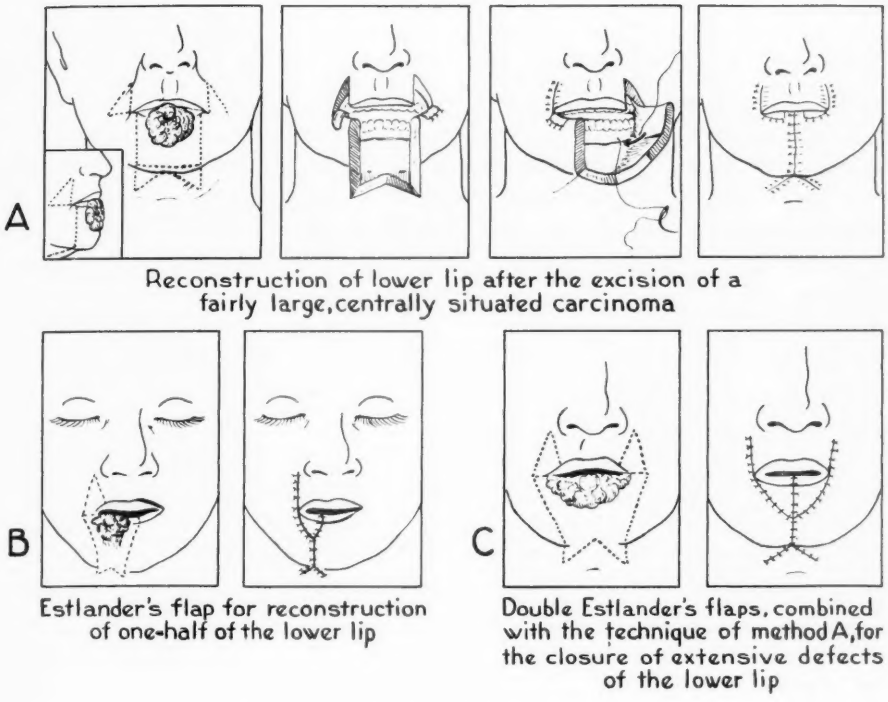

A
Reconstruction of lower lip after the excision of a fairly large, centrally situated carcinoma
B
Estlander's flap for reconstruction of one-half of the lower lip
C
Double Estlander's flaps, combined with the technique of method A, for the closure of extensive defects of the lower lip

FIG. 8.—Useful basic methods for cheiloplasty.

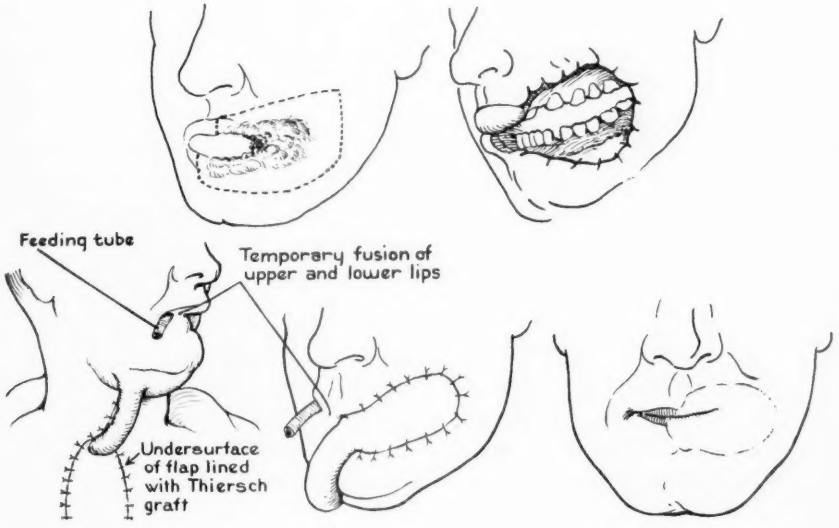


FIG. 9.—Variations in technic for the closure of large lip and cheek defects by the use of migrating tubed pedicle-flaps.

borders of the mandible, local infiltration must be added. By using conduction anesthesia, one eliminates most of the postoperative complications of a general anesthetic, and the patient is able to expel blood or clots from the oral cavity, thereby avoiding their aspiration into the trachea. Under a local anesthetic, the patient is also able to follow directions and to open or close the mouth, as necessitated by the various steps of the procedure.

In our experience, the plastic reconstruction of all or a part of a new lower lip is always best accomplished by the use of full-thickness flaps of the cheeks or of the upper lip, except in those cases where the defect is so extensive, by reason of removal of a portion of the cheek as well, that a transplant lined by a thick split or a Wolfe graft and nourished by a tubed-pedicle is constructed from the skin and subcutaneous tissue of the anterior chest wall or neck (Fig. 9). Operations utilizing unlined flaps of skin and subcutaneous tissue brought up from the neck or down from the scalp are of little practical value, since the raw surface within the mouth must heal by scarring and contracture, so distorting and shrinking the transplant as to result in both functional and cosmetic failure.

The most suitable source of tissue for the closure of lower lip defects is a lateral cheek flap from each side, which should be mobilized and drawn forward as far as possible, the closure being completed if necessary by flaps from the upper lip. In elderly subjects, the tissues of the cheeks will usually be found loose and relaxed, so that lateral cheek flaps may be advanced to close a defect 6–7 cm. in its lateral diameter. These flaps should always be drawn forward in a horizontal plane which is possible only if their lower edges are outlined by incisions made almost directly backward in the sagittal plane from the lower edge of the mandible into the submaxillary regions* (Fig. 8).

For moderate-sized lesions, Daland[16] forms rather narrow cheek flaps by lateral incisions placed well above the point of the chin, leaving an unnecessary amount of scarring in a prominently exposed position. In any case, such technic is suitable only to moderate-sized lesions, which could probably be more satisfactorily treated by radiation or by simple V-shaped excision. In larger lesions, if the lower borders of the lateral cheek flaps are formed by incisions running vertically downward into the submaxillary regions, even the defects left after excising the larger growths may be closed with only one prominently visible scar running downward from the vermilion border in the midline over the point of the chin, the remaining portions of the scar being rather inconspicuous below the edge of the mandible in the submental and submaxillary regions.

Another point in the forming of wide lateral cheek flaps, as illustrated

* Many text-books show the lower edge of such flaps outlined by incisions parallel to the lower border of the mandible, which is inclined obliquely upward and back. Flaps so outlined will be formed on the bias, so that they must be pulled not only obliquely forward but *also downward* in order to meet in the midline over the chin. This oblique tension will cause the newly formed lower lip to be pulled upward where it will eventually come to lie unnaturally under the upper lip.

in Figure 8 A, is to detach the soft tissues from the outer surfaces of the mandibles by sharp dissection and further posteriorly by subperiosteal dissection, freeing the masseter muscles from their attachments if necessary, preserving the integrity of the facial arteries. Within the mouth, the cheek flaps are mobilized by incisions in the lower gingivobuccal gutters which, if required, may extend posteriorly upward along the anterior edges of the ascending rami of the jaws. If lateral cheek flaps do not provide sufficient tissue for the complete closure of the defect, a satisfactory source of additional tissue is one Estlander flap (or sometimes two) from the upper lip (Fig. 8 B-C). The pedicle of such a flap may be cut down to a very narrow diameter (5 Mm.) provided that one preserves, intact, the superior labial (superior coronary) artery which runs very near the vermilion border. The fold of the pedicle then forms the new commissure of the mouth. Occasionally, in the excision of a moderate-sized lesion near the commissure, the defect may be completely closed by the use of one Estlander flap alone without mobilization of lateral cheek flaps.

If the defect is closed entirely by lateral cheek flaps, it will usually be found that the new lower lip is shorter than the upper lip, resulting in a "fish-mouth" deformity. This deformity may be overcome by excising Bernard[3] triangles from the cheeks and upper lip lateral to the commissure, as illustrated in Figure 8 A. The mucous membrane of these triangles is left attached at the base and sutured forward so as to form a part of the new vermilion border. This modification (Bernard) serves to set the labial commissures laterally and overcomes the redundancy of the upper lip while increasing the length of the lower. The tissues of the lips and cheeks possess a remarkable degree of elasticity and flexibility, and, therefore, the edges of the defect and the flaps may be molded and adjusted to an extent not possible in most other portions of the anatomy. Furthermore, the circulation of the tissues in this region is such that with a reasonable degree of care the nutrition of the flaps need cause no concern.

During the mobilization of extensive flaps from both sides, a large operative wound will necessarily be exposed to contamination and infection from oral secretions. Much of the contamination can be avoided if, in sponging the wound, care be taken that the oral secretions are not rubbed into the exposed raw surface. Constant suction should be maintained by an assistant so as to remove the saliva before it can run over on to the wound. As soon as the mucous membrane closure has been completed, the operative field should be repeatedly washed and irrigated with Dakin's solution while the external wound is being closed.

In suturing the edges, accurate approximation of both the skin and the mucous membrane is of utmost importance. This is particularly true of all suture lines within the mouth. Either the so-called dermal sutures or silk in two layers, one to the mucous membrane and one to the skin, makes a satisfactory closure. The mucous membrane closure is begun posteriorly in the gingivobuccal gutters, the first stitch being placed entirely on the gingival

side at the posterior limit of the incision. Subsequent sutures are placed about 0.5 cm. more anteriorly on the gingival than on the buccal side, and as each is tied, the mucosa is stretched more and more anteriorly so that eventually the tip of the flap will reach the midline. With reasonable care in suturing, the forward tension holds these flaps in such close approximation to the mandible that healing is usually by primary union. If the external wound edges can be drawn together firmly, there is seldom need for additional tension sutures even though the tissues appear to be very tightly stretched, since, after 24 hours, the flaps, which at first appeared to be under great tension, will have adjusted themselves so that there is no danger of separation. Healing of the skin should take place by primary union, so that the skin sutures can be removed a few at a time on the third, fourth, and fifth postoperative days. Those on the mucous surface may be left for a week or longer until the wound has healed firmly enough to permit wide opening of the mouth. Although the flaps may be very firmly applied to the outer surface of the mandible, some dead space usually persists in the wound in the submental and submaxillary regions. Adequate drainage by rubber tubes should be provided for irrigation by Dakin's solution for the first two or three days.

Wide excision with delayed closure may be indicated in certain cases. Long-standing cancer of the lip sometimes appears to be incapable of metastasizing, so that despite the rather discouraging appearance of a bulky, infected, widespread growth of the lip, there is no palpable evidence of cervical metastasis, which is the deciding factor in the selection of treatment in these cases. It is often found that such bulky lesions are movable over the mandible and that the involved portions of the lip and cheek may be completely removed, resulting in a large defect which may have to be left for delayed closure.

When no immediate closure of the defect is contemplated, the removal of a bulky infected lip cancer is usually best accomplished by a thin-bladed, actual cautery under general anesthesia. The red-hot cautery blade should be moved rapidly so as to control the capillary oozing without too much charring of the wound edges. Healing of the borders is hastened if the skin and mucous membrane edges are loosely approximated by interrupted sutures. After the border has healed, contraction results in a marked decrease in the size of the defect (Fig. 9), so that the later closure is facilitated. The most suitable form of plastic repair in such a case is a tubed pedicle-flap from the skin of the anterior chest wall or neck. If such a tube is taken from the neck, the necessity for at least one shift is obviated, but the cosmetic result is better if the entire tube is constructed from the chest wall, thereby eliminating all scarring of the neck. If its diameter is generous, such a tube, without any specially prepared transplant at its end, may be used alone to close fairly large defects (Fig. 10). In such instances, the tube is doubled or folded upon itself one or more times, in stages, across the defect. In other cases, at one end of a pedicle-tube a transplant can be raised from the chest wall and its inner surface lined with a thick split or

full-thickness graft from the thigh or inner surface of the upper arm. A transplant so prepared may be 6–7 cm. in diameter, and is indicated particularly when the defect involves the cheek. The possible variations in the form of such pedicle-flaps and in the detailed technics are almost infinite. We have

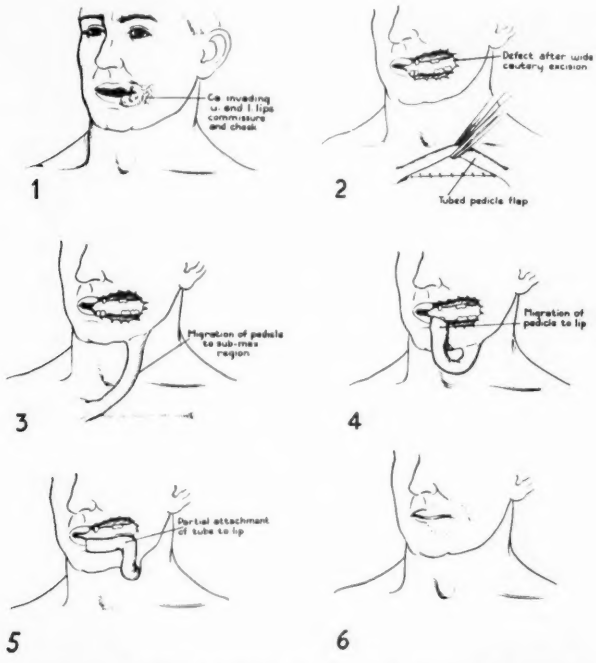


FIG. 10.—Alternate method for closure of large lip and check defects using a folded tubed pedicle without a specially prepared transplant.

successfully treated advanced, complicated lip cancer in this manner, in the presence of fixed inoperable submaxillary nodes, the latter being treated by a combination of fractionated roentgen radiation and radon seeds.

Occasionally, one may be justified in combining a limited dissection of the submental and one submaxillary triangle with a plastic operation of not too great extent. It is impractical and unsafe, however, to attempt an extensive or complete neck dissection at the same time as these large cheiloplasties. Neck dissection is unsuitable even following the healing of these cheiloplasties, since there is usually considerable scarring in the upper neck following the operation upon the lip. These large cheiloplasties find their greatest field of usefulness in cases of bulky primary lesions without cervical metastases.

General Principles in the Treatment of Metastases from Cancer of the Lip.—In any form of intra-oral cancer, the treatment of cervical metastasis is best considered as a problem entirely seperate from that of the primary lesion. From the practical standpoint, the subject may be considered under two headings: (1) The prophylactic treatment, or that which is given in the

absence of palpably demonstrable cervical metastases; and (2) the curative treatment of clinically positive metastatic nodes. It should be realized at the outset that the opinions which we express here concerning cervical metastasis in lip cancer do not necessarily apply to cervical metastatic nodes from intra-oral cancer in general. Metastases from lip cancer are more favorable from the standpoint of treatment and differ in many other respects from those in cancer of the tongue or of the nasopharynx.

Prophylactic Treatment for Cervical Metastases.—The term prophylaxis as used here refers to any treatment applied to the neck in the absence of clinically positive cervical nodes for the purpose of preventing the later development of metastases. To be exact, there is probably no method of prophylaxis against metastasis in any form of cancer except the early and successful eradication of the primary lesion. Once metastatic emboli have left the primary lesion and settled in lymph nodes, any treatment is curative rather than preventive. According to common usage, however, any treatment given before metastases are clinically evident, is termed prophylactic. At the Memorial Hospital it has been the policy for the last seven years to give no prophylactic treatment of any kind to the neck in intra-oral cancer if there is no clinical evidence of cervical metastases. The patients are re-examined at regular intervals, and only if actual metastases become clinically demonstrable is treatment given, and then with curative intent. The soundness of such a conservative plan of management should be judged on the basis of statistical analysis of the clinical behavior and the end-results in a series of observed cases as well as upon a theoretic evaluation of the merits of both radiation and surgery as related to this problem.

A survey of the literature reveals a wide divergence of opinion as to the proper methods of treatment for cervical metastasis. Some years ago, Pflüger[44] attempted to ascertain the prevailing opinion on this subject. He sent out questionnaires to representative surgeons, radiologists and dermatologists, and while the replies are interesting, the perspicacious observer will note that the opinions were undoubtedly conditioned by the specialties of the men who were questioned; that is, the surgeons, as a group, favored neck dissection, and the dermatologists favored nonsurgical methods. Radiation as a primary treatment was preferred by a few radiologists, and practically all of the radiologists advised postoperative radiation. As regards other published reports, few of the opinions expressed are based upon statistical analyses of observed clinical material and the end-results in unselected groups of cases. Some nonsurgical radiologists[2, 28, 43, 64] advise prophylactic irradiation in the absence of demonstrable metastases. Many surgeons[5, 20, 30] advise routine prophylactic neck dissection. Some[54, 62] believe that neck dissection alone is of value in the treatment of actual metastases, and there are those[17, 22, 30] who, in the face of rapidly accumulating evidence during the past ten years, sturdily maintain that metastatic cervical cancer has never been cured by radiation alone. It must be admitted that many of the old claims for radiologic cures of metastatic cervical nodes

were not well authenticated, since there was no histologic proof of the character of these nodes. In recent years, aspiration biopsy[37] has provided a means of obtaining tissue for histologic examination without surgical excision. While not all surgeons and pathologists accept the validity of this technical procedure, such a reactionary attitude is rapidly disappearing. At the Memorial Hospital, the accuracy of aspiration biopsy has been checked by subsequent excision of tumors in several thousand cases and, therefore, is no longer questioned.

An analysis of several hundred cases of cancer of the lip at the Memorial Hospital has shown that, despite the size of the primary lesion, of those patients admitted without palpable evidence of cervical metastasis and in whom the primary lesion was subsequently cured, only 8 per cent developed metastases during an observation period of five years. So-called prophylactic neck dissections, therefore, could not have had even theoretic value in 92 per cent of these cases, whereas under the higher reported mortality rates[30] following neck dissection about 11 per cent would have died of postoperative complications. The procedure would then have killed a greater percentage (11 per cent) than it could possibly cure (8 per cent). Even under the lower reported mortality rates (3–5 per cent), the risk would, obviously, still be unjustified since the postoperative deaths approach 50 per cent of the number (8 per cent) who could expect to benefit by the procedure. If no prophylactic neck dissections were performed, over 90 operations would be avoided in every 100 cases, and in the 8 per cent which later developed clinically demonstrable metastases, neck dissection would still give a very high, if not an equal, individual chance of cure. Under such considerations, what reasonable person, either lay or medical, would choose to undergo prophylactic neck dissection in lip cancer? The validity of these figures receives striking support from the observations of Taylor and Nathanson[58] who report that 247 patients with lip cancer without "palpable" lymph nodes were treated by excision of the primary lesion alone, with no primary treatment to the neck. Later, neck dissection was carried out in 25 cases because of the development of "palpable" nodes, and the nodes proved to be histologically positive in 20 of these (8 per cent of the total group). Richards[48] reports an even lower occurrence of subsequent metastases in cases without "palpable" lymph nodes on admission (three out of 244, about 1 per cent).

Even the ardent proponents of prophylactic neck dissection, apparently, do not practice it as routine, but modify the rigid theoretic indications by the somewhat arbitrary grouping of cases according to the size of the primary lesion or the "palpability" of cervical nodes. In any case, the percentage of histologically positive nodes in routine neck dissections is small. Kennedy[30] reports a collected series of 193 neck dissections in which 46 (24 per cent) were histologically positive. Figi,[20] in 549 prophylactic operations, found metastatic nodes in only 91 (16.5 per cent). In the latter series, the philosophically minded reader will be impressed by the waste of time and effort in the 458 cases in which the nodes were found to be negative for cancer.

He is bound to doubt whether the practice of neck dissection based upon such indications is reasonable, and to wonder whether or not more could have been accomplished in these cases, if an equal amount of time and money had been spent in treating cancer only where it was demonstrably present, and in palliating the suffering of other incurable cancer patients.

The contention of some surgeons that prophylactic neck dissections should be performed because of the impossibility of adequate follow-up is, in our opinion, a confession of indolence or of lack of organization. It must be admitted that, even after repeated efforts, not all cancer patients can be persuaded to return for systematic observation, but if the patient with lip cancer is negligent in this regard, the risk of recurrence is not entirely overcome by such prophylactic treatment, since the disease may recur in the neck even after neck dissection or in the lip itself. At the Memorial Hospital, only a small number of lip cases are lost to follow-up during the first two or three years, when the danger is greatest. Even up to five years the number of those traced reaches 95 per cent.

In the case of radiation, prophylactic treatment to the neck as ordinarily given does not carry with it any mortality, but if it cannot be demonstrated that such prophylactic irradiation is beneficial, then it must be conceded, at least, that it is wasteful from the economic standpoint even though otherwise harmless. As ordinarily advised and given, prophylactic irradiation in lip cancer consists of one to two S.E.D. (skin erythema doses) to both sides of the neck. Bergendal[2] administers only 2/3 S.E.D. Since such small dosage has never been observed—or at least reported—to sterilize a proven focus of epidermoid carcinoma, why should it be assumed capable of sterilizing an impalpable focus of cancer (the actual existence of which cannot be proved) simply because the patient survives and does not subsequently develop metastases? The same basic reasoning may be applied against the logic of pre- or postoperative radiation (if used in such doses). In the absence of palpable metastases, the administration of cancer lethal doses (six to eight S.E.D.) for prophylactic purposes to the entire lymph node bearing area of the neck has the same objections as prophylactic neck dissection; that is, we believe it to be entirely unjustified both from the standpoints of the deleterious local and constitutional effects and of the time and expense involved. Those who successfully apply radiation in the treatment of proven cervical metastases will readily concede that such treatment is unwarranted except when necessitated by demonstrable metastatic cancer.

Choice of Treatment Methods for Clinically Positive Cervical Metastases in Lip Cancer.—The selection of the particular form of treatment for metastases in lip cancer should be based upon the clinical features of a given case rather than any partisan preference for one or the other method. If the surgeon is also a radiologist, he is likely to take a broad view and to recognize that either radiation or surgery may possess unique advantages in individual cases and that often a combination of the two is superior to either employed alone. When adequate radiation facilities are at hand, it must be realized

that in the treatment of cancer the term "inoperable" is not synonymous with "incurable."

Radiation therapy does not find so wide an application in cervical metastases from lip cancer as it does in metastases from the more anaplastic, rapidly growing tumors of the tongue, extrinsic larynx, and nasopharynx. In lip cancer, the indications for radiation, rather than surgery, are about the same as in the general group of cervical nodes and include practically all inoperable nodes and those cases in which neck dissection would be difficult, dangerous, or of doubtful value because of the age and general condition of the patient. Adequate radiation therapy of metastatic cervical nodes has certain disadvantages, among them the fact that the immediate result is not so definite and that the method is more time-consuming than neck dissection. Radiation therapy must frequently be supplemented by surgery when the bulk or mass of metastatic cancer would necessitate dangerously large dosage, if treated by radiation alone. Among its advantages is the fact that when metastases are present on admission, radiation therapy may be administered without particular risk at the same time and in conjunction with irradiation of the primary lesion.

Depending on the individual case, either radiation or surgery may possess unique advantages. Despite recently published statements to the contrary, it must now be admitted that proven cervical metastatic nodes can be cured by radiation alone. Even in certain operable cases we have found this form of treatment superior to neck dissection. In the present series of lip cancer, 11 cases of histologically proven cervical metastases treated by radiation alone have survived five years. If the question should arise as to the percentage of cures obtained by the radiation treatment of cervical metastatic cancer, we wish to point out that it would be unfair to compare the end-results of radiation with those of surgical treatment, since all inoperable, recurrent, and advanced metastatic nodes receive radiation treatment for at least palliative purposes, whereas only the early and operable cases are treated by neck dissection. In the present series, 41 neck dissections were performed with one postoperative death (2.4 per cent). The excised tissues were positive, histologically, in 35 patients (85 per cent), of whom 13 (about 31 per cent) survived five years without recurrence.

In the final analysis, it is only fair to state that in the majority of cases of metastatic lip cancer, the selection of either radiation or surgery is optional. Neck dissection is probably more expedient when uncomplicated operable metastases occur at an interval after control of the primary lesion. When complicated metastases are present on admission, radiation or a combination of radiation and surgery is preferable to neck dissection. The general condition of the patient is occasionally the determining factor in the choice of treatment methods.

Neck Dissection.—A detailed description of the technic of neck dissection is beyond the scope of this paper. There are several principles of this

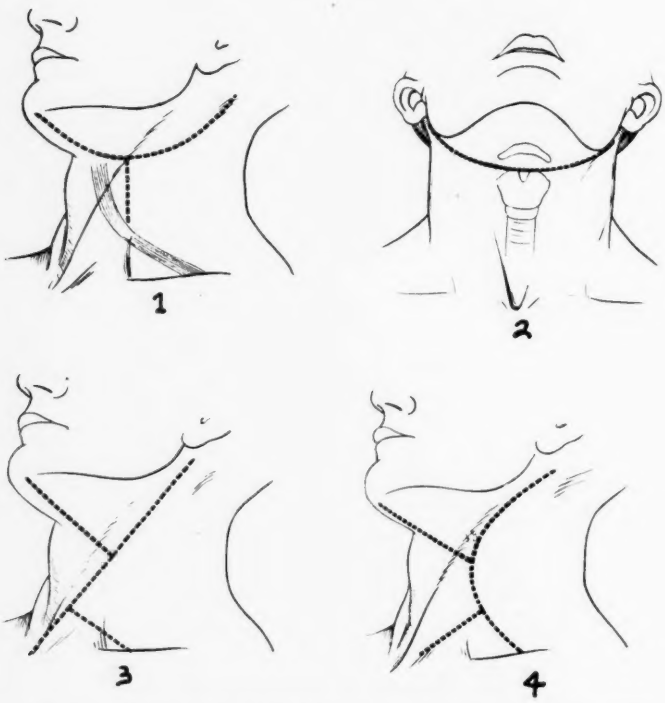


FIG. 11.—Useful forms of incision for neck dissection. (1) For supraomohyoid dissection. (2) For bilateral submaxillary and submental dissection. (3 and 4) For wide unilateral dissection extending to the clavicle.

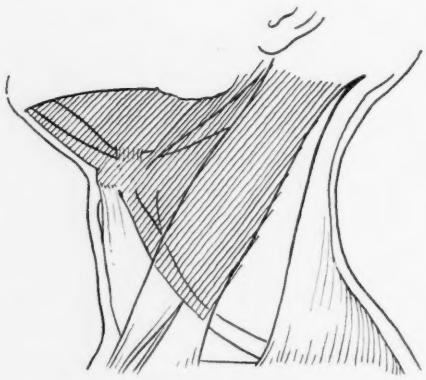


FIG. 12.—Extent of neck dissection in cancer of the lip, provided that metastases are not palpable, is below the level of the carotid bulb. If the middle or lower deep cervical nodes are palpably enlarged, the area of dissection should extend to the clavicle.

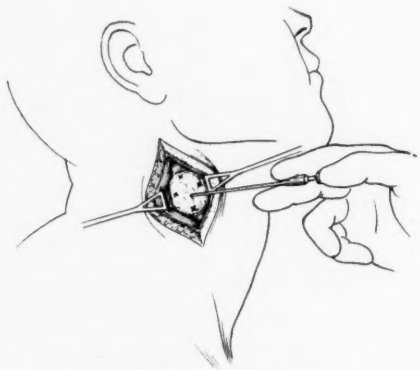


FIG. 13.—For supplementary irradiation of a cervical metastatic node by gold radon seeds, accuracy in the placement and distribution is favored by surgical exposure of the outer surface of the node.

procedure, however, which deserve mention. Four of the most useful forms of incision for neck dissection are shown in Figure 11.

The anesthesia, in practically all cases, should be local rather than general, since the higher mortality rates almost invariably are reported from those clinics where general anesthesia, usually rectal, is employed routinely. In properly selected cases, the mortality in neck dissection under local anesthesia should be practically zero. In cancer of the lip, the area of the neck dissection may properly be confined to the submaxillary, submental, and upper deep cervical regions above the level of the omohyoid muscle (Fig. 12). Unless the primary lesion involves the midline, the submental dissection may be limited to one side. Bilateral neck dissection at one sitting had best be limited to the submaxillary and submental regions. If the upper deep cervical areas are to be included, the procedure should be done in two stages at an interval of three to four weeks. The superficial and the deep planes of the dissection should be, respectively, the inner surface of the platysma muscle and the fascia of the deep muscles of the neck. It is best to remove the submaxillary salivary gland, the sternomastoid muscle, and the internal jugular vein. It is impractical to attempt to dissect out and preserve the eleventh cranial nerve. If there is palpable involvement of the middle deep cervical nodes, the area of dissection should extend down to the clavicle.

Radiation Methods for Cervical Metastases in Lip Cancer.—One of the most useful radiation technics is fractionated roentgen radiation given through a small portal directly over the node and followed by a supplementary dose of radon seeds. Under such a plan, there is a wide possible variation in technic. The dosage factors and technic described here refer to the employment of the following: 200 k.v., 0.5–1.0 Mm. Cu. filter, 35 cm. T.S.D., and portals 3–5 cm. in diameter. The treatment is designed to be given to a single node, to a group, or to each of immediately adjacent nodes. If the nodes are widely separated, it is best to treat each individually. Using portals 3–5 cm. in diameter (depending on the size of the node), the fractionated roentgen radiation is administered in daily or thrice-weekly treatments so as to administer 5,000–8,000 r in approximately 18–20 days; and immediately upon the completion of this radiation a supplementary dose of radon seeds is implanted, so calculated as to deliver six to eight S.E.D. into the tumor mass (Table II). This plan may be modified in the larger metastatic masses, 5–6 cm. in diameter, by fractionating the doses of radon seeds, implanting a lesser amount at weekly intervals during the course of fractionated roentgen radiation. The dosage factors under such modifications are largely empiric and must be learned by experience.

Radon seeds alone may be employed without preliminary external radiation, but the chances of success (especially in the larger masses) are not equal to those under the combination plan, since small errors in dosage and in the placement of the implants are much more significant than when part of the effect is obtained by external radiation. If gold radon seeds alone are employed, according to the method developed by Quick,[46] the dose is

calculated according to Table II, and should be larger, approximating ten S.E.D. in all cases. This method is often more useful and more expedient in the smaller nodes (less than 1.5 cm. in diameter).

TABLE II

MILLICURIES IN GOLD SEEDS REQUIRED TO DELIVER SPECIFIED DOSES TO MASSES OF VARIOUS DIAMETERS

	Diameter of Mass—Centimeters											
Skin Erythema Doses	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
	Number of Millicuries											
5	1.0	2.5	4.0	7.5	10	12	14	17	20	27	35	45
6	1.2	3.0	4.8	9.0	12	14	17	20	24	32	42	54
7	1.4	3.5	5.6	10	14	17	20	24	28	38	49	63
8	1.6	4.0	6.4	12	16	19	23	27	32	43	56	72
9	1.8	4.5	7.2	14	18	22	26	31	36	49	63	81
10	2.0	5.0	8.0	15	20	24	29	34	40	54	70	90
11	2.2	5.5	8.8	17	22	26	32	37	44	59	77	99
12	2.4	6.0	9.6	18	24	29	35	41	48	65	84	108

Radon seeds may be implanted through skin punctures, but their accurate placement is favored by surgical exposure, under local anesthesia, of the outer surface of the node (Fig. 13). Previously administered fractionated roentgen radiation to the node is no contraindication to surgical exposure, even though there is moderate blistering of the skin. Provided that the tissues are handled gently, healing is quite prompt when the incision is made through these blistered areas.

Combination of Surgery and Radiation for Cervical Nodes.—Combination methods are indicated particularly in the case of bulky, fluctuant suppurating metastases which are attached to the mandible. Such a lesion is usually inoperable, since its capsule has been perforated and the infected tumor has become attached to the periosteum of the mandible or to the deep muscle layers of the neck. Combination treatment may be given by applying heavy radiation (roentgenotherapy plus radon seeds in doses calculated to destroy the growth), following which the condemned mass of tissue, which would otherwise slough, is excised surgically, the wound, ordinarily, being left open to granulate and heal by secondary intention.

In other instances, the major portion of such a secondarily infected and perforated metastasis may be removed surgically by partial or total neck dissection and the infiltrated irremovable portion (often only 1–2 cm. in diameter) may be treated by the implantation of radon seeds. The detailed technic, especially with regard to radiation dosage in such cases, is too varied for detailed description.

COMPLICATIONS

Since the lip is not a vital structure, it is to be expected that serious complications seldom occur either as the result of the primary lesion or of its treatment. The most frequent treatment complication (7 per cent) in our series was persistent radiation necrosis at the site of the primary lesion following the implantation of radon seeds. In practically all instances, this

difficulty was due to injudicious dosage or incorrect placement of the implants. In all of these cases, surgical excision of the unhealed area resulted in subsequent healing. In nine cases (2 per cent) where radiation had been employed in the treatment of extensive growths of the lip or metastases under the edge of the mandible, localized osteomyelitis of the mandible developed, necessitating sequestrectomy. Such a complication is often unavoidable in the management of inoperable cancer. In the present series, there were seven postoperative deaths following extensive surgical removal of the primary lesion, the causes of death being pneumonia (two cases); lung abscess (two cases); heart failure (two cases); and septicemia (one case).

Recurrence.—Some of the apparent recurrences which take place after either radiation or surgical treatment are actually new cancers arising on other parts of the mucous membrane of the lip. In this series there were apparent recurrences in 22 cases following irradiation and two following surgical excision (6 per cent), and it has been impossible for us to determine exactly how many of these were actually second primary lesions. Of this group, subsequent treatment was successful in 16. Three died of other causes, and in only five of the 24 was treatment ultimately unsuccessful and death due to cancer. The elapsed time between treatment of the primary and the appearance of the second lesion or recurrence ranged from two months to seven years, with an average of 32 months.

FOLLOW-UP

Systematic follow-up of all cases is an integral part of the management of all forms of cancer, so that accurate information of the patient's clinical progress may be recorded for a period of at least five years. The surgeon who undertakes the treatment of a case of cancer places himself under a moral responsibility to keep the patient under observation during the period in which recurrence is likely to take place. For practical purposes, both the total period of observation and the intervals between examinations should vary with the relative malignancy of the anatomic form of the disease; as for instance, patients with cancer of the nasopharynx should be seen at shorter intervals than those with cancer of the lip. For statistical purposes, a five-year period of observation is required in all forms of cancer. In cancer of the lip, the customary intervals between examinations, at the Memorial Hospital, are indicated in Table III:

From the standpoint of the patient, the ostensible purpose of follow-up is the discovery and treatment of recurrences while the disease is still in a curable stage. From the scientific standpoint, another purpose, equally important, is the accumulation of definite knowledge of the progress of the patient and of his actual status at the end of a five-year period, when a final accounting of all cases is made. It is not sufficient that the physician should *believe* that the patient is well and free of disease simply because he has

heard nothing to the contrary. It is necessary to have factual evidence that the patient is alive and free from symptoms. If the patient has died before the end of the five-year period, it is essential to know the actual cause of death and whether there was clinical evidence of disease at the time. If he is living, it is essential to know whether he is free of disease or suffering from recurrent or metastatic cancer. Without dependable data in these respects, statistical reports of end-results have no value. In large series of cases there are, inevitably, some patients who refuse to make return visits and are subsequently lost track of. If they have been free of recurrence

TABLE III

INTERVAL BETWEEN EXAMINATIONS*

After Primary Treatment of Lesion	Frequency of Follow-Up Visits
During first 6 months	Every 1–2 mos.
During second 6 months	Every 2–3 mos.
During the second year	Every 3–4 mos.
During the third and fourth years	Every 3–6 mos.

* The shorter periods are to be preferred in all cases, but it is often necessary to compromise when the patient lives at a considerable distance, because of the effort, inconvenience, and expense of travel.

for a year or more before they disappear, they may fairly be termed indeterminate cases and subtracted from the total, thereby counting neither for nor against the end-results. If they are lost track of immediately following the initial treatment or before the end of a year, they must be counted as failures, whether or not they were free of disease when last seen. The investigator who subjects himself to such rigid discipline in calculating end-results will be stimulated to renewed effort in tracing lost patients.

Adequate follow-up is mainly a matter of organization and persistent effort. When a patient is discharged following the initial treatment, he should be given a definite future appointment for reexamination. If he does not return at the designated time, repeated appeals should be made by mail and by telephone to the patient himself, to members of his family, and to the referring physician. If these efforts fail, a personal visit by a social service worker may induce the patient to return, or at least furnish positive information as to his physical status. A single letter from the patient or a relative stating that he is free of disease is of little value, but continued reports and a final statement, after five years, that he is alive and well can be considered adequate. Before making the final calculations on a series of patients for five-year end-results, renewed attempts should be made to locate all untraced patients. Former addresses and telephone numbers should be checked. Relatives, friends, employers, or the referring physician should be questioned. If these sources reveal no information, local health boards may be appealed to for death records. Frequently an insurance company may be able to furnish pertinent facts. In series of cases now being analyzed at the Memorial Hospital, for which we have access only to these sources of information, we are able to locate between 90 and 95 per cent of all patients,

a proportion which biostatisticians have informed us is satisfactory for statistical purposes.

PROGNOSIS

Cancer of the lower lip is one of the least malignant forms of intra-oral cancer. Early lesions up to 1.5 cm. in diameter should be capable of cure in practically all cases following proper treatment if the patient is regularly observed and examined for recurrence. Failures often result from inattention to proper follow-up by either the patient or the physician. In this series, the average length of life of the unsuccessfully treated patient was about 38 months after onset. Certain factors influencing the cure rate, calculated on the determinate group, are given in Table IV.

TABLE IV

FACTORS INFLUENCING THE FIVE-YEAR CURE RATE IN 313 CASES (DETERMINATE GROUP) OF CANCER OF THE LIP OBSERVED AT THE MEMORIAL HOSPITAL

1928 to 1934, inclusive

	Total Number of Cases	Number of Five-Year Cures	Per Cent of Five-Year Cures
Age in Years:			
Below 40	38	31	89
40 to 49	63	45	71
50 to 59	86	57	66
60 and over	121	85	70
Not stated	5	1	
Metastases:			
None at any time	196	187	95
Present some time	117	32	27
Present on admission	90	22	24
None on admission	223	197	88
Developed after admission	27	10	27
Bilateral submaxillary	20	4	20
Histopathology (cases in which the primary was treated at Memorial Hospital):			
Squamous carcinoma Grade I	87	73	84
Grade II	143	102	71
Grade III	4	2	50
Grade IV	1	0	0
Ungraded	42	33	75
Spindle cell carcinoma	2	1	50
Size of Lesion:			
Under 1 cm.	33	33	100
1 to 1.9 cm.	118	102	86
2 to 2.9 cm.	49	35	71
3 cm. and over	60	33	55
Entire lip	5	5	100
Not stated	48	11	23
Position of Lesion:			
Upper lip	17	7	41
Lower lip	296	212	71
Associated leukoplakia	70	55	79
Associated syphilis	25	13	52
Primary cases (no treatment elsewhere)	228	175	77
Residual, recurrent or metastatic cancer after previous treatment elsewhere:			
After radiation alone	32	20	63
After surgery alone	30	12	40
After combination of radiation and surgery	6	2	33
After electrocoagulation or cautery	17	10	59
Total patients with residual or recurrent disease	85	44	52

Age and Sex.—From the analysis of the present series, it would appear that the prognosis is best below the age of 40 and over the age of 60. However, since the age-prognosis curve is rather irregular, we suspect that this variation is purely coincidental and that if the series were larger these deviations might be less evident. The treatment of cancer of the lip does not carry with it a high mortality rate, nor do we believe that the age of the patient markedly affects the malignancy of the individual tumor. Since the percentage of females with lip cancer is so small, no conclusive calculation of sex prognosis is possible.

Metastases.—Although not always so interpreted, the malignancy factor of any neoplasm depends almost entirely upon its capacity to metastasize. No better illustration of this fact can be found than in the prognosis of lip cancer. From Table IV, it is seen that of the cases which had no metastases at any time, the cure rate was 95 per cent. The failure to cure the remaining 5 per cent depended upon such infrequent occurrences as postoperative deaths, and those rather rare cases of inoperable and incurable, bulky tumors of the lower lip with no evidence of metastasis on admission. The presence of metastases at some time during the course of the disease reduces the cure rate to about 27 per cent. It would appear that the time of development of metastases has little influence on the prognosis, since the cure rate is about the same whether involved nodes are present on admission (24 per cent) or develop later (27 per cent).

Histopathology.—Our calculations of the histopathologic prognosis were made only upon those cases in which the primary lesion was treated at Memorial Hospital. Patients who were referred to our clinic with cervical metastases following cure of the primary lesion are not included, since the histologic grading of such cases is often uncertain. As would be expected, the prognosis is best in low grade squamous carcinoma and poorest with the higher Grades II and III.

Size of the Lesion.—When the primary lesion is less than 1 cm. in diameter, cure may be assured in almost all cases (100 per cent in the present series). As the size of the primary lesion increases, indicating a later stage of the disease and a greater chance of metastasis, the possibility of cure progressively diminishes, but it should be noted that even when the primary lesion is over 3 cm. in diameter, the chance of cure is still about 55 per cent. Curiously enough, in the five cases in which the entire lower lip was involved, the cure rate was 100 per cent. The good prognosis in these cases probably depends largely upon the fact that if the patient survives long enough for the primary lesion to involve the whole lip, the tumor is almost always of low histologic grade and apparently incapable of metastasizing, and, therefore, cure depends entirely upon control of the primary lesion.

Position of the Lesion.—Growths of the upper lip appear to belong to the group of spontaneous cancers, in contrast to those of the lower lip, in which chronic irritation is usually obvious as an etiologic factor. It is a common observation that such spontaneous cancers are highly malignant as

compared to irritation cancers. Such a theory is supported by the fact that of our 17 patients with primary lesions on the upper lip, only seven (41 per cent) survived five years.

Syphilis.—According to our statistics, the prognosis in lip cancer with associated syphilis (52 per cent cure rate) is less than the general average (70 per cent). Since the complications of treatment in lip cancer are so few, it is difficult to interpret this finding, which may be purely coincidental since the number of our cases with syphilis (25) is small.

Status on Admission with Regard to Previous Treatment.—Unsuccessful attempts at treatment reduce the possibility of cure in cancer of the lip, as shown in Table IV. The cure rate in those patients (primary cases) who did not receive previous treatment was about average, even when all-comers in all stages of the disease are included. The cure rate was only 52 per cent in the patients referred to us with residual and recurrent disease after unsuccessful treatment elsewhere. Despite the fact that the end-result statistics (70 per cent) could be improved (77 per cent) by the exclusion of such recurrent cases, it is obvious that the truth in regard to this disease is not revealed except by the inclusion of all clinical material.

END-RESULTS

In the present series, the net cure rate in 375 cases is 70 per cent (Table V). As we have previously mentioned, this series consists of a consecutive

TABLE V

FIVE-YEAR END-RESULTS IN CANCER OF THE LIP OBSERVED AT THE MEMORIAL HOSPITAL

1928 to 1934, inclusive

This series consists of all histologically proved cases of cancer of the lip, both early and advanced, admitted during the specified period. Only those patients are excluded who, for any reason, were unable to return for treatment, palliation, and observation in the Out-Patient Department, and those who were lost track of within the first month after no more than one or two visits (clinic shoppers).

Total Number of Cases		375
Indeterminate Group:		
Dead as a result of other causes and without recurrence	39	
Lost track of without recurrence	23	
Total number of indeterminate results		62
Determinate Group:		
Total number minus those of indeterminate group		313
Failures:		
Dead as a result of cancer	87	
Lost track of with disease	4	
Living with disease	3	
Total number of failures in treatment		94
Successful Results:		
Free from disease after five years or more		219
Five-year End-Results:		
Successful results divided by determinate group (219/313)		70%

group of all histologically proven cases of cancer of the lip, both primary and recurrent, which were admitted to our clinic during the years 1928–1934, inclusive. It is the policy of our clinic to accept all ambulatory patients with cancer, no matter how advanced the disease. If the patient is able and willing to return for treatment, palliation, or observation, the case is included

in our records for statistical purposes. Before calculating the net end-results in a given series, we substract only those cases in which an unfavorable outcome is not due to cancer, or in which the end-result is not definitely known because the patient was lost to follow-up after a year's freedom from disease. In the larger clinics, there are inevitably some patients lost track of, and such an allowance is, therefore, necessary. Such a policy of subtracting the indeterminate cases before calculating net end-results in cancer is followed in the large cancer clinics of the world (Radiumhemmet, Curie Institute). Biostatisticians whom we have consulted state that if at least 90 per cent of the cases in a series are accounted for, the calculations will be sufficiently accurate. In the present series, 93 per cent of the patients have been traced.

There is probably no anatomic form of cancer for which more end-results have been published than for cancer of the lip, but an attempt to compare our figures with those reported in the literature is disappointing. It is regrettable that so many reports, emanating from excellent clinics and made by undoubtedly competent surgeons and radiologists,[20, 23, 34, 38, 48, 55] should be unsuitable for statistical analysis. An outstanding fault in most publications is the lack of any standard, or definite, period of survival; as, for instance, a certain percentage of patients is said to have survived "from one to seven years,"[47] with no further data as to the number or proportion surviving for any given period. In many such unsatisfactory reports, it is obvious that the author has included a number of recent cases in an effort to make the total series as large as possible. Unfortunately, such attempts fail to accomplish the intended purpose, since all the figures are vitiated by the introduction of so much inconclusive material. How much more impressive it would be if accurate and conclusive results were given on a smaller group of consecutive cases, all observed for at least a five-year period. Many of the older reports and some of the more recent, even though otherwise suitable, are based upon three- rather than five-year survival periods. In other instances, one finds end-results calculated only on the patients treated with curative intent, without considering advanced cases for whom only palliative measures were possible. Other authors exclude cases recurrent after previous treatment elsewhere. There are also published calculations based upon only those patients "traced" with no accounting for those lost to follow-up, although in some of these the untraced cases make up almost one-fourth of the whole group. Some investigators begin by setting down a certain number of cases and then base their end-results on a much smaller number, with no explanation for the discrepancy. End-result statistics on "early cases," "cases without metastases," or cases "operated upon" are obviously calculated on highly selected groups and do not give the actual cure rate for cancer of the lip, but only the prognosis in various stages of the disease. In every instance, such grouping must necessarily be arbitrary, because any two surgeons would rarely agree exactly on the classification of all cases.

TABLE VI

PUBLISHED FIVE-YEAR END-RESULTS ON UNSELECTED CASES OF CANCER OF THE LIP

	Period Covered by Report	Total No. of Cases	Indeterminate		Determinate		Net Five-Year Cure Rate Percentage†
			Lost N.E.D.	Died of Other Causes	Died of Disease*	Five-Year Cures	
Berven[4]	1909–1923	179				(?)	64.2
Welsh and Nathanson[63]	1933	990‡	41		503	446	45
Lacassagne[31]	1919–1924	68		10	24	34	58
Schreiner and Mattick[53]	1914–1927	258§	19	32	140	94	40
Bergendal[2]	1914–1930	172	1	35	27	110	80
Martin, MacComb and, Blady	1928–1934	375	23	39	94	219	70

* This includes patients lost track of with disease and patients living with disease.

† Number alive and well divided by the number of the determinate group.

‡ Twenty untreated; counted as failures.

§ Four untreated; counted as failures.

The end-result statistics collected in Table VI are the only ones we have been able to find in which sufficient facts are given so that one can accept the stated cure rate, or so that one can calculate the net end-results from the data which are given. As compared to most serious forms of cancer, it will be seen that these end-result statistics are consistently high.

SUMMARY

This report is based mainly upon an intensive analysis of 375 consecutive cases of lip cancer, all histologically proved, admitted during the seven-year period 1928 to 1934, and includes all patients with cancer of the lip who applied to our clinic during that period, without exclusion of any because of an advanced stage of the disease. In the light of this material, cancer of the lip is discussed from the standpoints of etiology, pathology, symptoms, treatment, and prognosis. The net five-year cure rate in these 375 cases is 70 per cent.

BIBLIOGRAPHY

[1] Ahlbom, H. E.: Prädisponierende Faktoren für Plattenepithelkarzinom in Mund, Hals und Speiseröhre. Eine statistische Untersuchung am Material des Radiumhemmets, Stockholm. Acta radiol., **18**, 163, 1937.

[2] Bergendal, A.: A Review of 20 Years' Radium Treatment of Lip Cancer at the Radiologic Clinic, Lund, Sweden. Acta radiol., **19**, 103, 1938.

[3] Bernard, C.: Cancer de la lèvre inférieur opéré par un procédé nouveau. Bull. Soc. de chir. de Paris, **3**, 357, 1853.

[4] Berven, E.: Die Bedeutung der Elektroendothermie für die Strahlenheilkunde. Lazarus' Handb. d. Strahlenth., **2**, 996, 1931.

Idem: The Technic at Radiumhemmet in the Treatment of Tumors Except Cancer Uteri. Acta radiol., **10**, 3, 1929.

[5] Blair, V. P., Brown, J. B., and Hamm, W. G.: Radical Treatment of Carcinoma of the Lip. Am. Jour. Roentgenol., **29**. 229, 1933.

[6] Bloodgood, J. C.: Carcinoma of the Lower Lip. Surg., Gynec., and Obstet., **18**, 404, 1914.

[7] Brewer, G. E.: Carcinoma of the Lip and Cheek. Surg., Gynec., and Obstet., **36**, 169, 1923.

[8] Broders, A. C.: Squamous Cell Epithelioma of the Lip. J.A.M.A., **74,** 656, 1920.
[9] Burke, E. M.: Metastases in Squamous Cell Carcinoma. Am. Jour. Cancer, **30,** 493, 1937.
[10] Butlin, H. T.: Diseases of the Tongue. 1st ed., London, 1885; 2nd ed., 1900.
[11] Cary, N. A.: Frequency of Syphilis with Cancer of the Lip, Tongue, and Buccal Mucous Membrane. J.A.M.A., **75,** 858, 1920.
[12] Charache, H.: Contact Implantation of Cancer. New York State Jour. Med., **38,** 1400, 1938.
[13] Cowan, L. R.: Low Voltage Lightly Filtered Roentgen Radiation Versus Radon and High Voltage Roentgen Radiation in the Treatment of Superficial Cancer. Am. Jour. Roentgenol., **42,** 556, 1939.
[14] Crile, G. W.: Treatment of Malignancy. ANNALS OF SURGERY, **93,** 99, 1931.
[15] Cutler, M., and Buschke, J. F.: Cancer: Its Diagnosis and Treatment. Philadelphia and London, W. B. Saunders and Co., 1938.
[16] Daland, E. M.: Repair of Large Defects After Removal of Cancer of the Lips. Surg., Gynec., and Obstet., **69,** 347, 1939.
[17] Eggers, C.: Cancer Surgery; Value of Radical Operations for Cancer After Lymphatic Drainage Area Has Become Involved. ANNALS OF SURGERY, **106,** 668, 1937.
[18] Elliott, J. A.: Treatment of Epithelioma of the Lip by the Dermatologist. Arch. Dermat. Syph., **27,** 373, 1933.
[19] Estlander, J. A.: Méthode d'autoplastie de la joue ou d'une lèvre par un lambeau emprunte a l'autre lèvre. Rev. mém., méd., et chir., **1,** 344, 1877.
[20] Figi, F. A.: Recurring Epithelioma of Lower Lip and Chin; Diathermy and Cautery Excision; Reconstruction of Lower Lip. Surg. Clin. North America, **12,** 961, 1932.
Idem: Epithelioma of the Lower Lip; Results of Treatment. Surg., Gynec., and Obstet., **59,** 810, 1934.
[21] Filatoff, W.: Plastie a tige ronde. Westnik Oftalmol., 1917, Avril, Mai, Nos. 4, 5 (russe).
[22] Fischel, E.: Rational Therapy for Cancer of the Lower Lip. Am. Jour. Cancer, **15,** 1321, 1931.
Idem: Surgery as Applied to Lymph Nodes of the Neck in Cancer of the Lip and Buccal Cavity. Am. Jour. Surg., **24,** 711, 1934.
[23] Forssel, G.: On the Permanency of the Radiologic Healing in Malignant Tumors. Acta radiol., Supp. **2–4,** 7, 1928.
[24] Hall, W. C.: Radiation Treatment of Epithelioma of the Lip. Radiology, **38,** 116, 1937.
[25] Hay, A. W. S.: Cancer of the Lip and Mouth. Manitoba Med. Assn. Rev., **18,** 231, 1938.
[26] Janeway, H. H.: Radium Therapy in Cancer at the Memorial Hospital, New York (First Report, 1915–1916). New York, Paul B. Hoeber, 1917.
Idem: The Treatment of Cancer of the Lip by Radium. J.A.M.A., **70,** 1051, 1918.
[27] Janowsky, L. J.: Zur Frage des Lippenkrebses. Arch. klin. Chir., **65,** 329, 1902.
[28] Jovin, I.: Die Behandlung des metastatischen Krebses der Halslymphdrüsen. Strahlenth., **62,** 262, 1938.
[29] Kaplan, I. I.: Radiation Therapy of Malignant Lesions of the Lip. Radiology, **28,** 533, 1937.
[30] Kennedy, R. H.: Epithelioma of the Lip with Particular Reference to Lymph Node Metastases. ANNALS OF SURGERY, **99,** 81, 1934.
Idem: Epithelioma of the Lower Lip. ANNALS OF SURGERY, **106,** 577, 1937.
Idem: Malignancy of the Lower Lip. Surg. Clin. North America, **17,** 297, 1937.
[31] Lacassagne, A.: Les résultats de la curiethérapie des épitheliomas des lèvres. Arch. d'Electr. méd., **37,** 358, 1929.
[32] Lane-Claypon, J.: Report on Cancer of the Lip, Tongue and Skin. Reports on Public Health and Medical Subjects No. 59. London, His Majesty's Stationery Office, 1930.

[33] Loos: Zur Statistik des Lippenkrebses auf Grund von 565 Fällen aus der v. Brunschen Klinik. Beitr. klin. Chir., **27**, 57, 1900.

[34] Lund, C. C., and Holton, H. M.: Carcinoma of the Lip. Am. Jour. Roentgenol., **30**, 59, 1933.

[35] MacFee, W. F.: Early Grade I Carcinoma of the Lower Lip with Metastasis to the Cervical Lymph Nodes. Surg. Clin. North America, **18**, 535, 1938.

[36] MacMahon, J. S.: Squamous Cell Carcinoma of the Lip. Australian and New Zealand Jour. Surg., **7**, 40, 1937.

[37] Martin, H. E.: Cheiloplasty for Advanced Carcinoma of the Lip. Surg., Gynec., and Obstet., **54**, 914, 1932.

Idem: Treatment of Cancer of the Lip. Am. Jour. Surg., **30**, 215, 1935.

Martin, H. E., and Ellis, E. B.: Aspiration Biopsy. Surg., Gynec. and Obstet., **49**, 578, 1934.

Martin, H. E., and Stewart, F. W.: Spindle Cell Epidermoid Carcinoma. Am. Jour. Cancer, **24**, 273, 1935.

[38] de Monchaux, C.: Interstitial Radium Treatment in Carcinoma of the Lip: A Review of 71 Cases. Med. Jour. Australia, **2**, 221, 1937.

[39] Moreland, R. B.: The Treatment of Metastatic Carcinoma of the Neck Secondary to Carcinoma of the Lip. J.A.M.A., **110**, 1084, 1938.

[40] Most, A.: Die Topographie des Lymphgefässapparates des Kopfes und des Halses in ihrer Bedeutung für die Chirurgie, Berlin, 1906.

[41] Nystrom, G.: Kraftsjukdomarna i Sverige, Stockholm, 1922.

[42] Padgett, E. C.: Epidermoid Carcinoma Of and About the Oral Cavity. Int. Jour. Orthod, **22**, 283; 387; 504; 605; 716; 830; 939; 1040; 1157; 1255, 1936: **23**, 73, 1937.

[43] Pfahler, G. E., and Vastine, J. H.: Treatment of Cancer of the Lip by Electrocoagulation and Irradiation. J.A.M.A., **98**, 32, 1932.

Idem: Cancer of the Lip. Penn. Med. Jour., **37**, 385, 1934.

[44] Pflüger, O. H.: Treatment of Neck Nodes in Cancer of the Lip, Tongue and Mouth. Calif. and West. Med., **34**, 136, 1933.

[45] Price, L. W.: Metastases in Squamous Carcinoma. Am. Jour. Cancer, **22**, 1, 1934.

[46] Quick, D.: Interstitial Radiation in Metastatic Cervical Nodes of Epidermoid Cancer. ANNALS OF SURGERY, **93**, 380, 1931.

[47] Regaud, C.: Quoted by Bergendal[2].

[48] Richards, G. E.: Radiologic Treatment of Cancer (1929–1935). IV. Carcinoma of the Lips. Canad. Med. Assn. Jour., **35**, 490, 1936.

[49] Rouvière, H.: Anatomy of the Human Lymphatic System. Ann Arbor, Edwards Bros. Inc., 1938.

[50] Rowntree, C. W.: Malignant Disease of the Lips. A Statistical Study Based on the Records of the Middlesex Hospital. Arch. Middlesex Hosp., **7**, 118, 1906.

[51] Saemann, O.: Die Transplantations—Methode der Herrn. Prof. Dr. Burow. Deutsch. Klin., **20**, 221, 1853.

[52] Sassier, P.: Lymphatiques de la muqueuse labiale inférieure. C. R. de la Soc. Anat., in Ann. d'anat. path. et d'anat. norm. méd.-chir., **4**, No. 2, 935, 1927.

[53] Schreiner, B. F.: End-Results of Irradiation of Cancer of the Lip. Radiol. Rev. and Chi. Med. Rec., **51**, 187, 1929.

Schreiner, B. F., and Mattick, W. L.: Five-Year End-Results Obtained by Radiation Treatment of Cancer of the Lip. Am. Jour. Roentgenol., **30**, 67, 1933.

[54] Semken, G. H.: Surgery of the Neck. In Nelson's Loose Leaf Surgery, **2**, 763, 1927.

[55] Simmons, C. C., and Daland, E. M.: The Results of Operations for Cancer of the Lip at the Massachusetts General Hospital, from 1909 to 1919. Surg., Gynec., and Obstet., **35**, 766, 1922.

[56] Stewart, C. B.: Cancer of the Lip; Report of 88 Cases from the Steiner Clinic. Surg., Gynec., and Obstet., **53**, 533, 1931.

[57] Swinton, N. W., and Trommald, J.: Carcinoma of the Lip. Surg. Clin. North America, **18,** 599, 1938.

[58] Taylor, G. W., and Nathanson, I. T.: Evaluation of Neck Dissection in Carcinoma of the Lip. Surg., Gynec., and Obstet., **69,** 484, 1939.

[59] Trueblood, D. V.: A Discussion of Lesions of the Lip and Oral Cavity. West. Jour. Surg., **46,** 395, 1938.

[60] Usilton, L. J.: Personal communication.

[61] von Bruns, V.: Handb. d. prakt. Chir., p. 694. Tübingen: Laupp, 1859.

[62] Wangensteen, O. H., and Randall, O. S.: Treatment and Results in Carcinoma of the Lip. Am. Jour. Roentgenol., **30,** 75, 1933.

[63] Welch, C. E., and Nathanson, I. T.: Life Expectancy in Malignant Disease, Part II. Carcinoma of Lip, Oral Cavity, Larynx and Aŕtrum. Am. Jour. Cancer, **31,** 238, 1937.

[64] Widmann, B. P.: Carcinoma of the Lip: Results of Roentgen and Radium Treatment. Am. Jour. Roentgenol., **32,** 211, 1934.

[65] Wile, J. H., and Hand, E. A.: Cancer of the Lip. J.A.M.A., **108,** 374, 1937.

[66] Wörner, A.: Über die Endresultate der Operation des Lippenkrebses (v. Brun's clinic). Beitr. klin. Chir., **2,** 129, 1886.

PERFORATION OF THE CERVICAL ESOPHAGUS WITH THE FLEXIBLE GASTROSCOPE*

CASE REPORT—DIAGNOSIS—TREATMENT

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WITHIN RECENT YEARS, the hazards of endoscopic examination of the stomach and first portion of the duodenum have been greatly reduced by the use of the flexible gastroscope. Thus, a recent questionnaire by Schindler,[1] who devised the instrument, disclosed that only ten serious accidents had occurred in a total of 22,351 cases in which it had been employed. These accidents all consisted of traumatic perforations; eight involving the stomach, one the jejunum, and one the cervical portion of the esophagus. Only the last resulted fatally. In view of the apparent rarity of accidental perforation of the cervical portion of the esophagus with the flexible gastroscope, it appears warranted to report a case which presented a number of interesting and unusual features, and to discuss briefly the diagnosis and management of the condition.

Case Report.—B. L., white, male, age 40, was admitted to Mt. Sinai Hospital, September 23, 1940. The relevant history was one of recurrent episodes of abdominal pain, vomiting, and loss of weight, of approximately five years' duration. Six months previously, he had suffered a severe hematemesis. Diagnostic studies including gastric analysis and roentgenologic examination, performed in the Out-Patient Department, suggested the presence of a diverticulum of the first portion of the duodenum. In an attempt to clarify the diagnosis further, he was referred to the hospital as an ambulatory case, for gastroscopic examination.

On the day of admission, the Schindler flexible gastroscope was introduced under local anesthesia. The gastroscopist stated that after the instrument had been passed downward apparently without difficulty, for a distance of about six inches beyond the upper incisor teeth, a small amount of blood was noted in the patient's mouth. The instrument was withdrawn immediately, and it was noted that the flexible rubber bougie at the distal end of the apparatus was missing. Within a few moments the patient began to complain of pain over the right side of the neck; and palpation disclosed tenderness and crepitation in that area. Surgical consultation was requested immediately.

When first seen by the author, not more than ten minutes after the accident had occurred, the patient complained of severe pain on swallowing. Both sides of the neck were moderately swollen, especially the right. Bilateral crepitation was present and extended from the clavicle to the angle of the jaw. Tenderness was noted over the right side of the neck lateral to the larynx. The diagnosis of instrumental perforation of the upper esophagus was made and immediate operation advised. In order to ascertain whether the missing tip of the instrument had passed downward into the stomach or was lodged in the cervical region, roentgenologic examination was made while the operating room was being prepared. Films of the neck, with the patient in the antero-

* Presented before the Joint Meeting of the New York Surgical Society and the Philadelphia Academy of Surgery, February 12, 1941.

posterior and lateral positions, revealed extensive collections of air in the cervical tissue planes and in the retropharyngeal and retro-esophageal space (Figs. 1 and 2). On the right side, opposite the lower cervical and first dorsal vertebrae, the missing bougie was seen with its tip pointing *cephalad.*

Operation.—This was performed, under local anesthesia, approximately three-quarters of an hour after the accident occurred. An incision was made along the anterior border

FIG. 1.—Anteroposterior view. Note extensive subcutaneous emphysema, and air dissecting between the various tissue planes. The missing bougie lies at the root of the neck, with its distal end pointing *cephalad.* Note the distance between the bougie and the trachea. The button over the right clavicle lies on the skin.

of the right sternomastoid muscle, from a point above the level of the larynx down to the suprasternal notch. The sternomastoid muscle and carotid sheath were retracted laterally, the anterior belly of the omohyoid traversed, and the margin of the right lobe of the thyroid gland exposed. The latter then was mobilized and retracted medially to expose the lateral aspect of the esophagus.

Everywhere within the operative field the areolar tissue between the muscle planes was distended with bubbles of air. No discoloration was noted however. The missing tip of the gastroscope was discovered at the root of the neck, alongside the esophagus, and was removed. The esophagus was then exposed freely and inspected. About two inches above the level of the foreign body an irregular laceration, approximately one-half inch long and with everted edges, was found in the right posterolateral esophageal wall. In view of the fact that the edges of the defect were bruised and ecchymotic it was deemed unwise to close the latter by suture. Accordingly, a small iodoform packing was placed down to the opening and brought out at the lower angle of the incision. Another small iodoform packing was placed alongside the esophagus, at the entrance to the superior mediastinum, and was also brought out through the lower part of the wound. The subcutaneous tissues and skin were closed loosely with interrupted sutures.

An intravenous infusion of 1,000 cc. of 5 per cent glucose solution was begun after operation, and a Levin tube was introduced into the stomach for purposes of feeding. Sulfanilamide was administered, in 1 Gm. doses every four hours, for 48 hours. The packing which had been placed down to the esophageal laceration was shortened on the third postoperative day and removed the following day. The lower packing was shortened on the fifth day, and removed 24 hours later. The Levin tube was removed on the

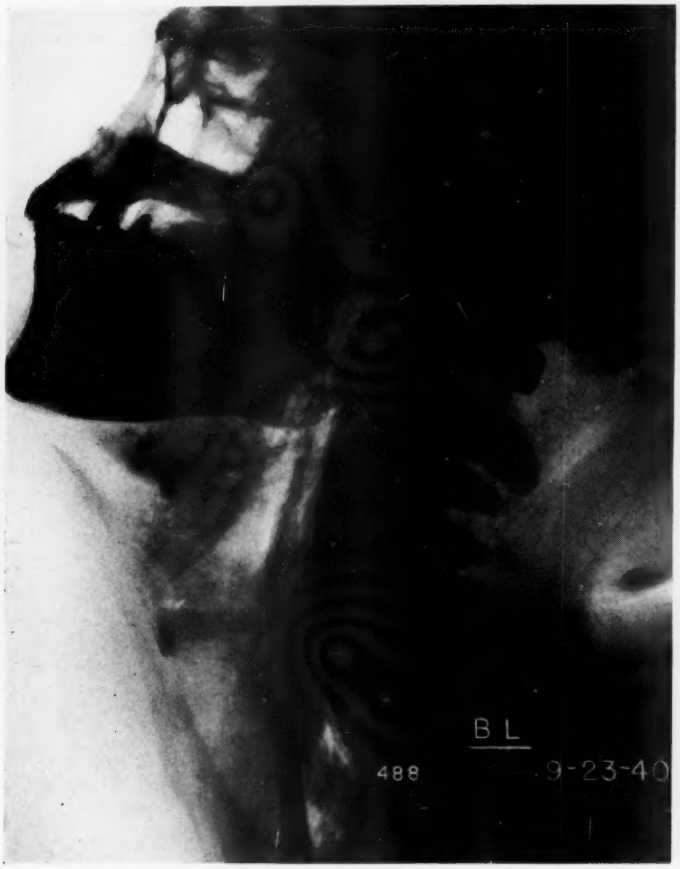

FIG. 2.—Lateral view. Note particularly, air in the retro-esophageal and retro-pharyngeal spaces; and the widening of these areas. Air extends upward to the base of the skull. The bougie lies anterior to the esophagus, and lateral to it (as demonstrated in the anteroposterior view).

sixth postoperative day; and the patient placed upon a soft diet, which he took without difficulty. Convalescence was uneventful; and he was discharged on the eighth postoperative day, with the wound healed. At no time following operation was there evidence of leakage from the esophagus.

Five weeks later, barium studies revealed slight irregularity in the outline of the posterolateral surface of the esophagus at the site of previous injury. No other abnormalities were noted. At the present time (five months after operation) the patient is entirely free of symptoms referable to the esophageal trauma, and roentgenologic examination of the esophagus is negative (Fig. 3).

COMMENT.—The rubber bougie, which forms the tip of the flexible gastroscope, is cemented to the adjacent metal portion of the instrument, and

is also fixed to it by wire which is incorporated within its substance. Its position when found in the periesophageal tissues, with its distal end pointing *cephalad*, would seem to indicate that the bougie became sharply angulated at its point of junction with the metal portion as the instrument was being

FIG. 3.—Four months postoperative. Roentgenogram taken after administration of a thin barium mixture. Note the normal contour of hypopharynx and esophagus, and normal retropharyngeal and retro-esophageal spaces.

passed. The result was that the metal end, no longer protected by the soft bougie which normally advances ahead of it, penetrated the esophageal wall and passed into the tissues of the neck. In view of the fact that the gastroscopist reported that no difficulty had been encountered, and that undue force had not been employed as the instrument was passed, the bougie could have become so sharply angulated only if it were loose. Its complete detachment, outside the esophagus, probably occurred as the instrument was being withdrawn.

Discussion.—Personal observation of 20 cases of accidental perforation of the cervical portion of the esophagus, both by instruments and ingested foreign bodies (usually chicken and fish bones) has demonstrated that all such lesions are not only potentially serious but are often a threat to life. Because of the direct anatomic continuity between the retro-esophageal space and the posterior compartment of the superior mediastinum, the most common cause of death is mediastinal infection. The initial periesophageal infection may assume the form of a phlegmon, or of an abscess. A phlegmon is usually

a diffuse lesion which displays little tendency to localize and quickly extends downward into the mediastinum. An abscess, on the other hand, usually begins as a fairly well-localized lesion; but unless evacuated fairly promptly may subsequently extend downward into the mediastinum. The following case cited by Schindler,[1] although not observed by him personally, illustrates this point well:

In brief, four hours following gastroscopy, with the flexible instrument, the patient developed symptoms consisting of pain in the neck, dysphagia and fever. Marked swelling about the left side of the neck and subcutaneous emphysema (*indicative of actual perforation of the esophagus**), were detected next morning. Because of "improvement" in the patient's condition soon thereafter, conservative therapy was employed. On the eighth day, however, the diagnosis of "abscess of the left hypopharyngeal region" was made. On the next day, the patient developed dyspnea and cyanosis; necessitating an emergency tracheotomy. As the trachea was exposed, large quantities of pus welled into the wound and the patient succumbed on the operating table. The significant findings at autopsy consisted of a perforation of the posterior esophageal wall at the level of the seventh cervical vertebra and an adjacent large mediastinal abscess. The case illustrates very well a frequent result of the conservative treatment of patients with gross perforations of the cervical portion of the esophagus.

At the present time, a difference of opinion exists in regard to the treatment of traumatic perforations of the cervical portion of the esophagus. The chief disagreement appears to center about cases in which the perforation appears to be small, and those in which there is doubt as to whether penetration of the esophageal wall is complete. It has been demonstrated that, in certain cases, a cervical periesophageal abscess may evacuate itself spontaneously into the esophagus through the original pathway of injury, or may be evacuated into the esophagus by endo-esophageal instrumentation. While, unquestionably, such a fortunate outcome may, at times, be noted, personal observation has indicated that it is the exception rather than the rule; and that more frequently the infection extends downward into the mediastinum and results in the patient's death. While it is not the purpose of this communication to discuss, at length, the treatment of actual small perforations or suspected perforations of the cervical esophagus, it may be stated, categorically, that the patient's interests are best served by prompt external surgical exploration rather than by a policy of "watchful waiting." Thus, if actual perforation is present, adequate surgical drainage may be afforded. On the other hand, if the penetration of the esophagus proves to be incomplete, exploration, as described, is a relatively simple procedure which is well tolerated by the patient.

In contradistinction to small perforations or suspected perforations of the cervical portion of the esophagus, there can be little discussion concerning

* Italics mine (A. S. W. T.).

the necessity for prompt operation in cases of gross perforation associated with subcutaneous emphysema or with roentgenologic evidence of air in the periesophageal tissues. In such cases the likelihood of serious consequences is great, since leakage of infected material from the esophageal rent is apt to be more free and pathways of extension of infection are opened, as air dissects its way along the tissue planes, especially in a downward direction. In cases in which subcutaneous emphysema is not noted, the diagnosis of perforation can be made on roentgenologic examination of the neck. Films should be taken in the anteroposterior and lateral planes, with the patient in the erect position. The lateral view is particularly important, in so far as it is the only one in which the retropharyngeal and retro-esophageal space can be visualized. Since air escaping from the upper esophagus enters these areas first, the visualization of the latter is essential to early diagnosis. It is to be emphasized that the quantity of air seen in the retropharyngeal and retro-esophageal space need not be great and that the presence of only a bubble or two suffices to establish the diagnosis.

Once the diagnosis of perforation has been made, prompt operation, consisting of exposure and treatment of the esophageal rent through an external cervical incision under local anesthesia, is recommended. As has been stated previously, it is fully appreciated that at times certain patients may recover following more conservative therapy. However, should a patient under conservative therapy develop a descending infection of the mediastinum, as happens not infrequently, the surgical problem becomes much more complicated and the prognosis considerably more grave. In view of these dangers and the negligible risk involved, there appears to be little question as to the wisdom of early operative treatment.

SUMMARY

An unusual case of accidental perforation of the cervical portion of the esophagus with the flexible gastroscope, is presented. The rubber bougie, which constitutes the distal portion of the instrument, became detached and remained lodged in the neck after the gastroscope was withdrawn. The diagnosis of free perforation of the esophagus was made clinically, and confirmed by immediate roentgenologic examination, which disclosed a large quantity of air in the soft tissues of the neck and the missing bougie lying free in the periesophageal tissues at the root of the neck. Prompt operation was performed through an external approach, the foreign body removed, and the perforation cared for. Recovery was uneventful, the patient being discharged eight days after operation, with the wound healed. When last observed, approximately five months after operation, he was entirely free of symptoms referable to the esophageal trauma and roentgenograms were negative.

REFERENCE

[1] Schindler, R.: Am. Jour. Dig. Dis., 7, 293, July, 1940.

DISCUSSION.—DR. JOHN B. FLICK (Philadelphia, Pa.).—I have operated upon two patients for mediastinal suppuration following esophagoscopy. They illustrate what may happen when periesophageal infection occurs following injury to the cervical esophagus and operation is delayed. Both were operated upon late, following the injury. Their histories are of some interest and will be recited briefly. The first patient, a female, age 46, had a bronchoscopy and esophagoscopy performed September 1, 1936. These examinations were negative except for a tendency to spasm at the level of the cricopharyngeal muscle on passage of the esophagoscope. That evening, her temperature rose to 102° F., and she developed pain in the region of the sixth cervical vertebra. The following day, she had some substernal pain and her leukocytes rose to 15,500. From then on, until after operation, she had a septic temperature. I saw her 25 days after the esophagoscopy, and, under local anesthesia, through a posterior incision, with resection of segments of the fourth, fifth and sixth ribs, drained a large mediastinal abscess on the right side. Ultimately, she made a complete recovery.

The second patient, a female, age 59, had an esophagoscopy performed, under general anesthesia, May 4, 1938. The following day her temperature rose to 102° F.; her leukocyte count to 19,000; and she complained of pain in her neck, back and chest. She had difficulty in swallowing, and dyspnea. Because of dyspnea, a tracheotomy was performed, but the dyspnea was not relieved. I saw her seven days after the esophagoscopy, and, under local anesthesia, exposed the upper ribs posteriorly, on the right side. The patient, already in desperate condition, died soon after the operation was begun. However, exposure was continued.

An abscess was opened and foul-smelling pus and gas, under pressure, escaped. A finger introduced into the abscess cavity could be passed across the bodies of the vertebrae to the left side. The abscess cavity extended upward to the level of the first rib and downward to the level of the fifth rib posteriorly. The esophagus could be seen and had been pushed forward. The pleural cavity was not opened. On further examination, with a finger in the abscess cavity and the other hand palpating the base of the neck on the right side, it was evident that the abscess could have been drained by an incision similar to that employed in exposing a diverticulum of the esophagus. The drainage, however, would not have been as satisfactory as through the posterior exposure.

Many surgeons have called attention to the necessity for early drainage through the neck in cases of injury to the cervical esophagus, yet this is by no means always undertaken. Gabriel Tucker has warned of the presence of osteophytes on the bodies of the cervical vertebrae in some individuals which predispose to injury to the esophagus during esophagoscopy. He insists upon lateral roentgenologic studies of the cervical spine in all patients before esophagoscopy. Too much stress cannot be put on the necessity of early operation and drainage through the neck in cases of injury to the cervical esophagus. Drainage should be undertaken as soon as injury and infection are suspected, and before a mediastinal abscess has developed. A rising leukocyte count; emphysema in the tissues of the neck; and a rising temperature following trauma due to instrumentation, or to foreign body, are sufficient evidence to warrant operation.

The use of sulfanilamide and of zinc peroxide should be of value in treating these infections.

ACTUAL HOLDING POWER OF VARIOUS SCREWS IN BONE

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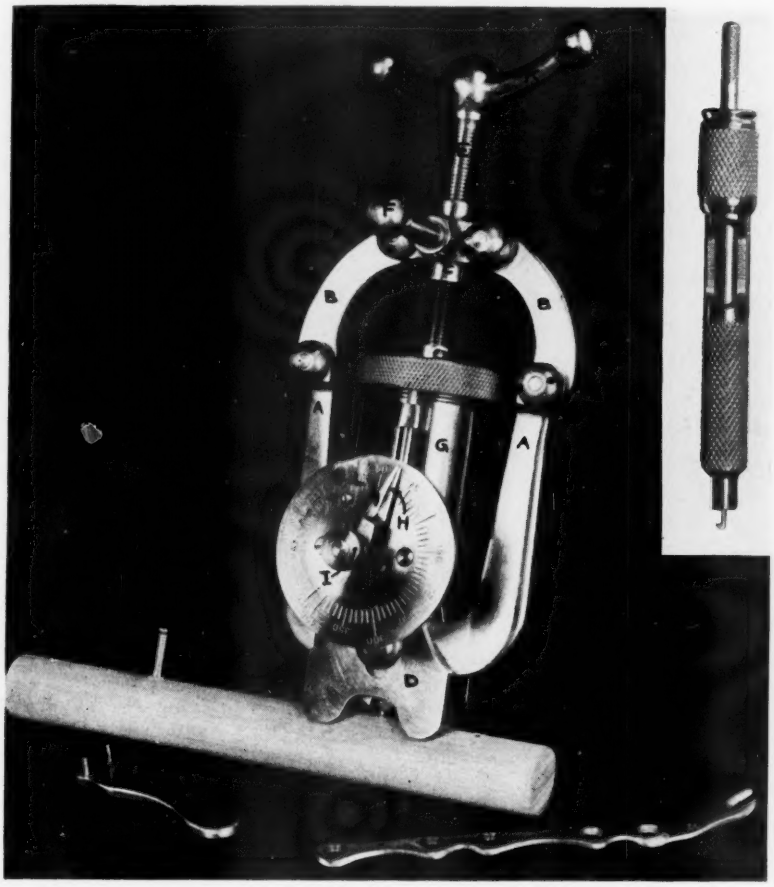
IN THE CONVICTION that most of the difficulties encountered in bone plating are mechanical rather than surgical or physiologic, a comprehensive study was undertaken of the factors involved. The first phase of the work was reported[1] in December, 1938, wherein a simple jig was described for centering the drill point in the hole of a plate. The jig also acts as a very effective depth gauge. The present discussion has to do with the actual holding power of various screws in bone, the determination of the correct drill size for each of the screws, and the effect of time on the holding power of the vanadium, stainless steel, and Vitallium screws.

The Method.—The evaluation of the holding power of screws has, in general, been relatively subjective and inexact. It was expressed in terms of ease of application—whether the screw went in with much or little resistance. By its very nature, this was an inexact determination and merely the indication of an impression. We have made this determination an exact one. At first, plates made of spring steel were bent so that with the screws seated the spring of the plate would exert a pull on the screws. Several of these plates were put in dogs with different screws at either end. This method was soon abandoned because the plates, which were made of high carbon steel, corroded and broke. It was then decided to use a noncorroding plate of Vitallium, after cutting a section from the bone. In this manner, the whole weight of the dog was transmitted through the screws. Thus it was possible to show in an indirect way that the end of the plate with fine threaded screws broke loose more frequently than the end plated with the coarse threaded screws. But again this method was inexact and resulted in a high dog mortality.

Finally, it was suggested that a method of extracting screws from bone be devised which would measure the pull required. Such an instrument was constructed by an interested group of engineers (Fig. 1). It consists of a vise-like pair of arms which grasp the head of the screw, pulling on the screw as force is applied to the threaded handle. This pull is transmitted through a heavy spring, the force exerted being indicated on a dial. By means of this machine, a pull of 525 pounds could be exerted and, after being calibrated accurately in a physical testing laboratory, an exact measure of the holding power of the screws was possible. As first constructed, this screw puller was capable of only 325 pounds pull, as we had thought this would be sufficient. Then it was increased to 425 and finally to 525 pounds. Even then we were unable to extract some screws anchored in only one cortex of a human bone.

When this method was first used, it was discovered that there was occa-

sionally a wide variation in holding power of a given screw in the shaft of the same bone, despite the fact that the same size drill was used and the screws were applied with equal ease. An additional variable which had not been controlled was the thickness of the cortex. After several attempts, a depth gauge was devised which measures the thickness of the cortex with an accuracy



EXTRACTOR USED IN ESTIMATING THE HOLDING POWER OF THE VARIOUS SCREWS

FIG: 1.—The device as shown by the photograph consists of a pair of sliding jaws (A), connected by links (B) and a cross-head (C); a stationary rest (D); screw (E); handle (F), and a tested spring balance (G). The spring balance is provided with a set pointer (H) for noting the maximum load. For a test, the set pointer is first brought into zero position by turning the knob (I). The device is then placed in proper position over the screw to be tested. The screw is gripped and tension on the screw is applied by turning the screw handle (K); the pointer (L) then indicates the pressure in pounds by means of rack and pinion to the dial. When the screw is extracted, the pointer (L) will move back to the zero position, but the set pointer (H) will remain in place to show maximum load in pounds.

FIG. 2.—(insert) Depth gauge which permitted an accurate measurement of the thickness of the cortex through each drill-hole, before a screw was inserted.

of 1/64 inch (Fig. 2). Readings are taken directly from the center piston. A lock screw at the top of the instrument permits readings after removing the micrometer gauge from the bone. It will be seen later that a slight varia-

tion in cortical thickness may make a large variation in the holding power of the screw, 0.093 inch altering the holding power as much as 80 pounds.

We have determined the actual measurements of the several screws used in this study and have indicated the theoretically ideal drill size (equal to the root diameter). Table I gives the outside diameter, the root diameter, threads per inch, and the theoretically ideal drill size.

FIG. 3.—Frequently, the screws did not just pull out on being extracted, but like the one here shown, helped themselves to a "button" of bone. Obviously, the holding power of such a screw is the strength of the cortex of the bone.

It would be impractical, and useless, to give the details in regard to all the 1,000 and more screws pulled during this study, but illustrative experiments will be presented. By means of the method described, the holding power of different types of screws was determined in the fresh animal, cadaver, and human bones, either following autopsy or amputation. Then the ideal drill size for each screw was determined, as well as a series of extractions showing the holding power when root size drills were used.

Holding Power in Dog Bones Using Root Size Drills.—The absolute holding power of four different screws was determined in the bones of freshly killed dogs, and the relative holding power of the different screws compared with special reference to any difference between the fine and the coarse threaded screws. Table II indicates the holding power in one cortex, the thickness of the cortex in 1/32 inch, and the holding power per 1/32 inch. All these readings are in pounds.

TABLE I

Screw	Diameter Outside Size	Diameter Root	Threads Per Inch	Root Size Drill
Vitallium (fine)	0.138 in.	0.104 in.	32	37
Vitallium (coarse)	0.144 in.	0.104 in.	20	37
Sherman	0.134 in.	0.102 in.	30	37
Zimmer	0.166 in.	0.104 in.	18	37
Parker-Kalon	0.137 in.	0.097 in.	20	41
Venable Stuck	0.136 in.	Tapered	18	..
Wood	0.120 in.	Tapered	20	..

TABLE II

Screw	Actual Holding Power	Thickness of Cortex	Holding Power Per 1/32 in. of Cortex
Vitallium (fine)	141 lbs.	3/32 in.	47 lbs.
Sherman	204 lbs.	4/32 in.	51 lbs.
Vitallium (coarse)	156 lbs.	3/32 in.	52 lbs.
Parker-Kalon	300 lbs.	4/32 in.	75 lbs.

These results show very little difference between the fine and coarse threaded Vitallium screws and do not confirm our supposition that coarse threaded screws (in the case of Vitallium) should hold more than a fine

threaded screw. Nevertheless, when the Sherman or Vitallium fine screws are compared with the coarse Parker-Kalon screws, a very definite difference is noticed. The similarity in holding power of the two Vitallium screws is due, we believe, to the nature of Vitallium. This particular alloy is so hard that it cannot be machined. Consequently, it has to be cast and the screws do not have as sharp cutting edges, so their insertion into a small hole is more difficult.

We believe the greatest advantage of the coarse, and, therefore, deeper threaded screws, is in their larger allowance for variation in the size of the hole in the bone. Carnes[3] has made enlargements of photographs of drill-holes in bones and they are seldom round. It is humanly impossible to hold either the bone or the drill absolutely stationary, and it is obvious that the finer the threads of the screw the more accurate the drill-hole must be to obtain anything like a maximum engagement of bone.

Holding Power in Cadaver Bones.—The tibia and humerus of a well-preserved cadaver were used in this experiment, which was designed to demonstrate the difference between fine and coarse threaded screws in human bone, using a root size drill. Again it was difficult to insert the Sherman fine screws, but the Parker-Kalon coarse screws uniformly went in well (Table III).

TABLE III

Screw	Actual Holding Power	Thickness of Cortex	Holding Power Per 1/32 in. Cortex
TIBIA			
Sherman	240 lbs.	5/32 in.	48 lbs.
Parker-Kalon	375 lbs.	5/32 in.	75 lbs.
HUMERUS			
Sherman	180 lbs.	4/32 in.	45 lbs.
Parker-Kalon	500 lbs.	5/32 in.	100 lbs.

In this experiment, as in all others presented, the figures given are average figures—averages of at least six screws extracted from each bone. In the cadaver experiments, the Parker-Kalon screws uniformly caused marked splintering of bone when extracted, while the fine screws left a smooth hole. Several of the Sherman screws stripped the bone while being inserted. These were not included in the averages shown.

Holding Power of Screws in Fresh Human Bone.—Screws were applied in the femora of a man, age 76, who had died two hours previously. He had been bedridden for six months with a carcinoma of the prostate. His emaciation was extreme. In this series, as in others, a minimum of six screws of each type was used (Table IV).

The Vitallium screws were difficult to apply well in this experiment. One of the Vitallium screws broke at the head during extraction at 260 pounds. Even though there was considerable demineralization, as demonstrated roentgenologically, the holding power of these screws was high, the coarse threaded stainless steel screws holding considerably more than the coarse Vitallium

TABLE IV

Screw	Actual Holding Power	Thickness of Cortex	Holding Power Per 1/32 in. Cortex
Vitallium (fine)	240 lbs.	5/32 in.	48 lbs.
Vitallium (coarse)	270 lbs.	5/32 in.	54 lbs.
Sherman	245 lbs.	5/32 in.	49 lbs.
Zimmer	350 lbs.	5/32 in.	70 lbs.
Parker-Kalon	335 lbs.	5/32 in.	67 lbs.
Venable-Stuck	260 lbs.	4/32 in.	65 lbs.

screw. The Venable screw held well in this experiment, and went in well (Fig. 3).

Holding Power in Child's Bone.—We were fortunate in obtaining the recently amputated leg of a girl age eight. These determinations were made on the lower third of the child's tibia, which had been amputated for osteogenic sarcoma (Table V).

TABLE V

Screw	Actual Holding Power	Thickness of Cortex	Holding Power Per 1/32 In. Cortex
Vitallium (fine)	75 lbs.	3/32 in.	25 lbs.
Sherman	126 lbs.	3/32 in.	42 lbs.
Zimmer	153 lbs.	3/32 in.	51 lbs.
Parker-Kalon	168 lbs.	3/32 in.	56 lbs.

The holding power of screws is definitely less in a child's bone, particularly with the fine threaded screws.

Machine Screws Versus Wood Screws.—The machine-type screw was long ago advocated for bone work by Sherman. Nevertheless, wood screws are still being used, for the very good reason that they are easy to apply. However, it seems to us that a wood screw is poorly designed for holding plates, at least, because of its taper. In applying any screw, it is necessary to drill a hole approximately equal to the root diameter at the base of the screw. If the drill-hole be smaller than this, the bone is subjected to undue pressure resulting in fracturing or pressure necrosis. This results in a loss of holding power. However, with a drill-hole equal to the root diameter at the base of a tapered screw, the threads near the tip will not engage any bone and the screw will suffer a loss of holding power. To confirm these views, a number of screws were extracted from human bone, using machine screws and ordinary wood screws (Table VI).

TABLE VI

MACHINE SCREWS *Parker-Kalon*			WOOD SCREWS		
Actual Holding Power	Cortical Thickness	Holding Power Per 1/32 In. Cortex	Actual Holding Power	Cortical Thickness	Holding Power Per 1/32 In. Cortex
400 lbs.	10/32 in.	40 lbs.	240 lbs.	10/32 in.	24 lbs.
350 lbs.	9/32 in.	39 lbs.	160 lbs.	8/32 in.	20 lbs.
420 lbs.	10/32 in.	42 lbs.	180 lbs.	7/32 in.	26 lbs.
400 lbs.	8/32 in.	50 lbs.	140 lbs.	8/32 in.	17 lbs.
	43 lbs. average			22 lbs. average	

These results do not agree with Hawley's[4] conclusion that tapering screws hold best, but he insists the threads must be wide and deep, the screws long and penetrating; these factors are so essential that they more than outweigh any slight loss from the tapering of his screws.

Cortical Versus Cancellous Bone.—All our determinations, up to this point, have been made upon the cortex of the bone, where the majority of screws are used in surgery. However, the use of screws around joints is becoming more common, and we were anxious to discover the difference in the holding power of the screws in porous bone as compared to compact cortical bone. Table VII shows a striking loss of holding power in cancellous bone as determined upon a human leg. Here, it is obvious that the coarsest possible thread is advisable to insure any appreciable holding power.

TABLE VII

Screw	Actual Holding Power	Depth of Insertion	Holding Power Per 1/32 in. Cancellous Bone
Sherman	64 lbs.	16/32 in.	4 lbs.
Parker-Kalon	144 lbs.	16/32 in.	9 lbs.
Zimmer	224 lbs.	16/32 in.	14 lbs.

It was also found that if only the thin overlying cortical bone was drilled and the screw allowed to cut its own way into the cancellous bone, the holding power of the screw was nearly doubled.

Correct Drill Size.—The correct drill size is a factor of major importance, since the holding power of a screw is in direct proportion to the amount of bone engaged by the threads. When we attempted to find authentic data on drill size, we were surprised by the paucity of information in the literature, and the complete omission of this subject from the catalogues of the various manufacturers of surgical supplies. Apparently, it was omitted because it was not known. One of the things we have tried to evaluate, therefore, is the optimum drill size for each screw.

From a theoretic standpoint, it seemed to us that the correct drill would be one which made a hole equal to the root diameter, or shank of the screw. A drill larger than this would reduce the amount of bone engaged by the threads and a smaller one would make insertion of the screw impossible. The only screw commonly used in bone work for which a drill size is mentioned (Sherman's) has a root diameter of 0.102 inch, and an outside diameter of 0.138 inch. The drill size recommended by him is a No. 32, measuring 0.118 inch, which leaves but 0.020 inch of thread to engage bone, or about 55 per cent of the total thread depth. Cotton[2] recommends for this screw a No. 30 drill, having a diameter of 0.128 inch. The discrepancy here results in a loss of some 70 per cent of potential holding power.

It was difficult, or next to impossible, to start some of the screws with a drill as small as the root diameter. These screws were inserted under ideal conditions, with the bone well-exposed and held firmly. Such conditions do not obtain in the operating room where fractures are difficult to hold and wounds deep. We wished, therefore, to determine the optimum drill size for

each screw, one which permits easy application and affords maximum holding power.

Extractions were made from a series of drill-holes, varying in size from the root diameter to approximately the outside diameter of the screw. These were done in fresh dog and human bones; the results with the two types of bone, while varying in total holding power, correlated nicely (Table VIII).

TABLE VIII

DETERMINATION OF OPTIMUM DRILL SIZE

Holding Power in Pounds Per 1/32 In. Cortical Bone with Various Drills

Drill Size	**37**	**36**	**35**	**34**	**33**	**32***	**31**	**30**	**29**	Holding Power with Optimum Size Drill
Sherman	46	58	46	58	58	**62**	**62**	47	36	62
Vitallium (fine)	45	45	50	50	**62**	**60**	**62**	50		62
Vitallium (coarse)	50	50	51	48	**60**	**60**	**60**	53		60
Zimmer	70	68	70	72	70	**75**	**75**	70		75
Parker-Kalon	71	70	72	**80**	75	60	64	52		80
Venable-Stuck (9/64 in.)	16	15	**18**	**18**	17	16	13			18
Drill Size	**47**	**46**	**45**	**44**	**43**	**42**				
Venable-Stuck (7/64 in.)	15	**17**	16	15	14	14				17

* Drill sizes over columns containing highest numbers (in bold faced type) afforded maximum holding.

Each drill was checked by a micrometer, and a variation of 0.002 inch to 0.00 inch was found. While it seemed correct, theoretically, to use a drill size equal to the root diameter of the screw, it became obvious that this size drill made the application of most of the screws too difficult for practical purposes. This was particularly the case with the fine threaded screws and the Vitallium screws—not as apparent with the Zimmer and Parker-Kalon screws.

In most cases, there was an actual increase in the holding power of the screws when an optimal rather than root size drill was used, although the former is always slightly larger. Probably this is because the larger drill makes the application of the screw easier and less likely to cause stripping of bone as the screw is inserted.

Another fact brought out in Table VIII, which seems important to us, is the variation in holding power of the Vitallium and Sherman screws as compared to the stainless steel coarse screws, as different sized drills are used. This further emphasizes the point made above, namely, with the Vitallium and Sherman screws the application is difficult with small drills and one screw may go in well while the next may be inserted only with great pressure. To insure good application with these screws the larger size drills are necessary.

The effect of time on the holding power of these screws is seen by the curves shown in Chart 1, which are self-explanatory. It is obvious that loss in holding power with either stainless steel or Vitallium screws is too slight to be of clinical significance, particularly, when we keep in mind the fact that most fractures which are immobilized in fair position exhibit bony union in eight weeks. Table IX shows the percentage of loss in holding power at the end of ten weeks, after which screws will have served their purpose.

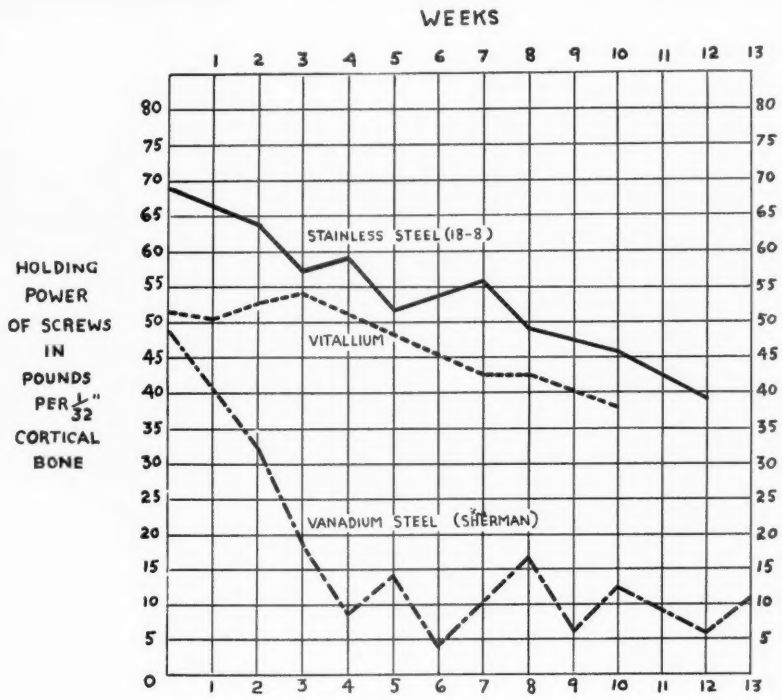

WEEKS
1 2 3 4 5 6 7 8 9 10 11 12 13
80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
HOLDING POWER OF SCREWS IN POUNDS PER 1/32" CORTICAL BONE
STAINLESS STEEL (18-8)
VITALLIUM
VANADIUM STEEL (SHERMAN)

CHART 1.

TABLE IX

EFFECT OF TIME ON HOLDING POWER OF SCREWS

Type of Metal	Initial Holding Power in Lbs. Per 1/32 in. Cortical Bone	Change in Holding Power by Weeks													Percentage Loss of Holding Power in Ten Weeks
		1	2	3	4	5	6	7	8	9	10	11	12	13	
Vanadium steel..	49	40	34	19	9	14	4		17	7	13		5	11	74%
Vitallium.....	52	51	53	54		48		43	43		38				27%
Stainless steel...	69		64	57	59	51		56	49		46		39		34%

Table X shows drill measurements, and is included here for convenience.

TABLE X

Drill No.	Diameter in Inches
47	0.0785 in.
46	0.0810 in.
45	0.0820 in.
44	0.0860 in.
43	0.0890 in.
42	0.0935 in.
—	—
37	0.1040 in.
36	0.1065 in.
35	0.1100 in.
34	0.1110 in.
33	0.1130 in.
32	0.1160 in.
31	0.1200 in.
30	0.1285 in.
29	0.1360 in.

Our screw puller was not designed for, nor capable of, pulling the screws used in fixation of fractures of the femoral neck; the strength of these devices has been thoroughly investigated by Compere.[5]

SUMMARY AND CONCLUSIONS

The variable mechanical factors of applying metal screws in bone have been discussed with the view of discovering the possible sources of error and failure in obtaining maximum holding. Sufficient data has been presented to demonstrate our conviction that the mechanical aspects of this engineering problem are of great importance. While it has been shown that a coarse threaded screw is superior in holding power to a fine threaded screw, it has also been shown that the character of the metal employed modifies this difference. Particularly, with cancellous bone, it is evident that the coarser threads are more advantageous. A series of original determinations have been made to ascertain the correct drill size for the screws tested (Table XI).

TABLE XI

Screw	Correct Drill Number	
Sherman	31 or 32	
Vitallium (fine thread)	31 or 32	
Vitallium (coarse thread)	31 or 32	The larger size should be used in especially hard bones, otherwise the smaller is recommended.
Zimmer	31 or 32	
Parker-Kalon	33 or 34	
Venable-Stuck (9/64 in.)	34 or 35	
Venable-Stuck (7/64 in.)	35 or 36	

The holding power of screws made of stainless steel or Vitallium does not diminish sufficiently in ten weeks to be of clinical importance.

If the various factors are carefully controlled, six screws used in applying a plate to a "normal femur," set through both cortices, could resist a pull of as much as one and one-half tons!

Since the Zimmer Manufacturing Company have changed their screw sufficiently, since our work was done, the results as recorded do not now apply.

REFERENCES

[1] Hand, Fred E., and Lyon, Will F.: An Improvement in the Application of Bone Plates. ANNALS OF SURGERY, **108**, 1118, 1938.

[2] Cotton, Frederic J.: Fractures. Lewis' Practice of Surgery, Vol. II, Chap. 4, p. 18.

[3] Carnes, James A.: Personal communication.

[4] Hawley, George W.: Personal communication.

[5] Compere, Edward L.: To be reported.

MORBID INFLUENCES IN INTESTINAL OBSTRUCTION AND STRANGULATION

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INTESTINAL OBSTRUCTION remains one of the most rapidly lethal of surgical diseases. Scudder, Zwemer and Whipple,[29] in 1938, studied a series of 2,150 cases of acute intestinal obstruction and strangulation collected from a number of sources. When herniae and tumors had been excluded from that series, there remained 632 cases, of which 45 per cent had proved fatal. In spite of phenomenal progress in other branches of abdominal surgery, the mortality of acute intestinal obstruction remained at a high, and almost unchanged, level for more than 30 years after the beginning of the present century, and the disease is still a challenge both to the surgeon and to the experimentalist.

The incalculable number of experiments in intestinal obstruction which have been performed during the last quarter of a century have, however, not been fruitless. As a direct result of animal and clinical experimentation, two powerful new weapons have been added to our therapeutic armamentarium—the nasal suction tube and the intravenous saline drip. Powerful as these weapons are, it is wise to realize their limitations. Nasal drainage and intravenous saline are beneficial in most cases of acute intestinal obstruction, and may be continued with benefit for days in simple occlusion of the bowel, for example, and in adynamic ileus. In cases of strangulation, on the other hand, the need for operative relief is much more urgent. It is often difficult to distinguish simple occlusion from strangulation clinically, and to persist with conservative measures in a case of internal strangulation is to court disaster. I have been impressed by more than one case of adhesive obstruction, treated by suction drainage and saline infusion for 24 hours or more, only to present at operation a strangulated and devitalized bowel; 24 hours of delay may mean the difference between viability and gangrene. It is conceivable that, while the present vogue for prolonged preoperative decompression and saline administration may be expected to reduce the mortality of simple intestinal occlusion, it may actually lead to an increase in the mortality of internal strangulation.

Even in simple occlusion of the bowel, patients still die with sufficient frequency to raise the suspicion that we have something yet to learn of the lethal mechanism of the disease. It may be that our administration of saline is too haphazard and inexact; dosage formulae, such as those elaborated in the Department of Surgery of the University of Michigan,[14] certainly merit wider adoption. Whatever the explanation, frequently a patient suffering from intestinal obstruction is lost in spite of preoperative nasal suction drainage, in spite of forced intravenous salines, and in spite of an apparently successful operation. In these fatal cases, the chloride content of the blood may be at or

Submitted for publication September 2, 1939.

near a normal level just before death. One is forced to the conclusion that depletion of water and chlorides is not invariably the sole lethal factor.

In the literature of intestinal obstruction, there is a frequent conflict of theories, and even of experimental observations. This is in great part due to the complexity of the subject. Intestinal obstruction is not a single disease, but a group of diverse diseases; a theory of the cause of death in duodenal occlusion is not applicable to volvulus of the sigmoid colon. It follows, therefore, that each variety of obstruction must be separately studied, and the more exact our pathologic classification is, the more accurate are our observations and deductions likely to be.

The following classification is sufficiently inclusive for clinical purposes, and detailed enough to be a basis for experiment. It must be remembered, however, that pure forms of obstruction, though easily produced in the experimental animal, are relatively rare in clinical practice. In strangulated hernia, for example, the strangulated loop is also a closed loop; the bowel above the strangulation is occluded at the hernial ring, just as in low small intestine obstruction; ultimately, the whole small intestine dilates above the obstruction, and the vomiting of high obstruction is superadded upon the effects of a relatively low obstruction; finally, after relief of the strangulation, the affected loop of bowel may fail to recover its peristalsis, and we may have strangulation, small intestine obstruction, closed loop obstruction, and adynamic ileus all present together in a single case. Of these various forms, one usually predominates, and attracts surgical attention before the other forms have time to exercise their full pathologic effect. In rapidity of effect, strangulation takes precedence over closed loop obstruction, closed loop obstruction over simple occlusion of the lumen, and high occlusion over low occlusion.

CLASSIFICATION OF TYPES OF OBSTRUCTION

A. Simple Occlusion of the Lumen:
   (1) High occlusion of the small intestine.
   (2) Low occlusion of the small intestine.
   (3) Colonic occlusion.

B. Closed Loop Obstruction:
   (1) Sterile loops.
   (2) Heavily infected loops.
   (3) Mildly infected loops.

C. Strangulation:
   (1) Short loops.
   (2) Medium loops.
   (3) Long loops.

A. SIMPLE OCCLUSION

(1) *High Small Intestine Occlusion.*—High small intestine occlusion is the one form of intestinal obstruction in which experimental and clinical study has been completed. In consequence of the work of Maury, Hartwell and Hoguet, Haden and Orr, Elman and Hartmann, Armour, Jenkins, Wangen-

steen, and a host of other workers, it is now recognized that all the phenomena of high small intestine obstruction are dependent upon the loss to the organism of water and of inorganic ions which, poured into the stomach and duodenum in enormous quantities as digestive juice, fail to pass beyond the obstruction to be reabsorbed, as they normally are, by the intestine below. The progressive loss of water leads to an increasing dehydration, which is manifest clinically in the dryness of the patient's skin, the increasing thirst, and the diminution in urinary output. The blood becomes increasingly concentrated, the red cell count and the hemoglobin rise, and there is an increase in blood viscosity and sedimentation rate.

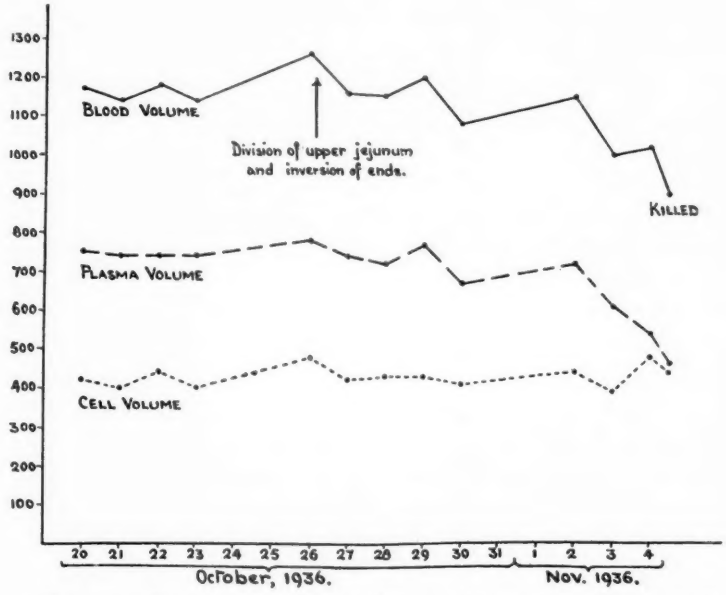


CHART 1.—Showing the terminal depletion of blood volume in an animal subjected to high small intestine occlusion. The reduction in blood volume is wholly due to a fall in plasma volume, the result of dehydration. (By permission of the British Journal of Surgery)

TABLE I

DOGS SUBJECTED TO HIGH SMALL INTESTINE OCCLUSION

The terminal reduction in blood volume is in each case due to a loss of plasma. (By permission of the British Journal of Surgery)

No. of Exper.	Level of Occlusion	Duration of Life	Mean Blood Volume (Cc.)	Reduction in Blood Volume (Per Cent)	Reduction in Plasma Volume (Per Cent)	Reduction in Cell Volume (Per Cent)
1	Terminal duodenum.....	5 days	1,030	25	43	—
2	Below ampulla.....	11 days	1,160	14	33	—
3	Below ampulla.....	6 days	1,360	23	44	7
4	Terminal duodenum.....	13 days	1,400	30	47	—
5	Terminal duodenum.....	9 days	1,180	44	32	—
6	Below ampulla.....	17 days	1,400	18	31	—

These striking effects of high small intestine occlusion may even alter the blood volume, and they alter it in a very characteristic way. Just before death, there is a remarkable reduction (Chart 1) in the volume of circulating blood. If Table I is studied, it will be seen that the terminal declension of the whole blood volume of dogs subjected to occlusion of the duodenum or upper jejunum is determined wholly by a reduction of the volume of the plasma, and that the volume of the red cells remains unaltered. It is profitable to compare this table with the blood volume tables of low small intestine obstruction and of strangulation (Tables IV and VII).

Dehydration is accompanied by demineralization. The chloride content of the blood and tissue fluid falls, and chlorides virtually disappear from the urine. In an attempt to maintain the total electrolyte content of the blood, bicarbonate is withheld in the circulation; the bicarbonate content of the blood is demonstrably elevated, and the carbon dioxide combining-power is increased. Alkalemia is thus established. Meanwhile, as a direct result of the general dehydration, there is an increase in protein catabolism, and, before death, an elevation of the nonprotein nitrogen of the blood. The whole morbid sequence, dehydration, demineralization, alkalemia, azotemia, is too familiar to require further elaboration here, and is fully proved by a mass of clinical and experimental observation.

It is in the treatment of high small intestine occlusion (and in a less degree this applies to pyloric occlusion) that duodenal drainage and the intravenous saline drip have their most dramatic effect. In clinical practice, high small intestine occlusion in its purest form is seen in such conditions as postgastrojejunostomy vomiting, when a loop of jejunum running to or from the stoma becomes kinked, and all the duodenal juices are vomited; or in obstruction of the upper jejunum by bands or adhesions in the upper part of the root of the mesentery. Rarer varieties of obstruction at this level are duodenal ileus, volvulus neonatorum, congenital atresia of the duodenum or duodenojejunal junction, and herniation into the paraduodenal fossae or lesser sac in the upper abdomen.

Most high obstructions are due to simple occlusion of the lumen, and only occasionally does one of the upper loops of small intestine become strangulated. It must, however, be remembered that there are no clinical features to distinguish high occlusion from internal strangulation of one of the upper loops of jejunum. In cases of high intestinal obstruction, there is always a possibility that the obstructed loop is a strangulated loop. In consequence, unless the cause of obstruction is definitely known, and unless strangulation can be definitely excluded, it is unwise to continue duodenal drainage and intravenous saline infusion over too long a period; the restoration of water and chloride should be rapid, for strangulation may be present, and the need for operation is then urgent.

(2) *Low Small Intestine Occlusion.*—This form of obstruction, the commonest clinical variety, has proved a complex problem for both the experimentalist and for the clinician, and it is safe to say that the precise cause of

death is not known. There are a number of factors probably responsible for the deterioration in the patient's condition in most cases, and it is possible that the predominant cause of death may vary from case to case. Most of the available data concerning intestinal obstruction have been obtained from the experimental animal. It should be remembered, however, that the cause of death of an animal suffering from untreated obstruction is not necessarily the same as the cause of death of a patient whose obstruction has been relieved by operation. Our patients suffering from acute obstruction are now invariably treated by operation, and deaths from acute intestinal obstruction now are postoperative deaths. We, of this generation, have virtually no experience of low small intestine obstruction untreated by operation, and our only knowledge of the full, fatal course of the untreated disease is obtained from animal experiment.

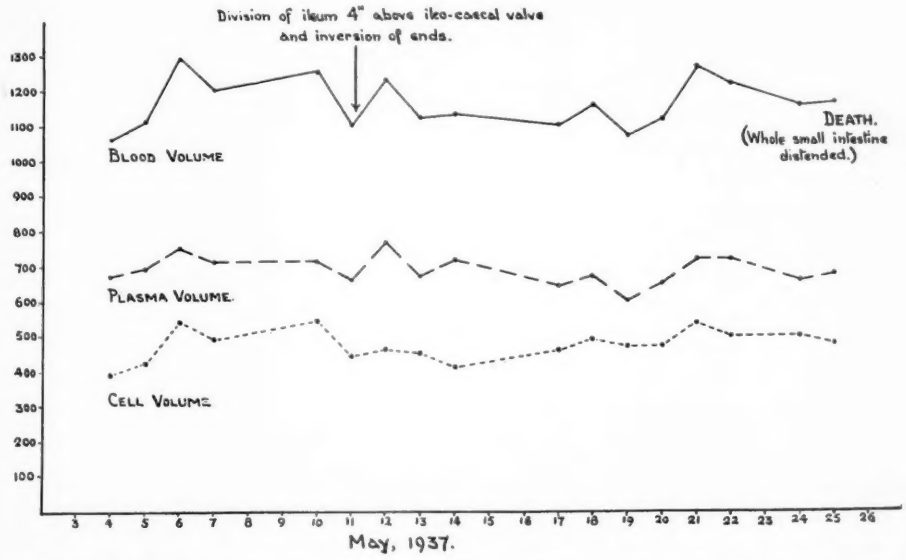


CHART 2.—Low small intestine occlusion in the dog: Showing no reduction in blood volume, plasma volume, or cell volume at the time of death. (By permission of the British Journal of Surgery)

During the last century, before operative relief became the standard treatment of acute intestinal obstruction, the patient suffering from acute, low small intestine occlusion died, as a rule, toward the end of the third, or during the fourth week of his illness. The duration of life then was the same as it is in the untreated experimental animal to-day. Even the patient suffering from internal strangulation lived into the second or third week after the appearance of symptoms. To-day, the sufferer from low obstruction comes under the surgeon's care after a few days or, at most, a week of illness; his obstruction is relieved, and, if he dies, he dies within 24 to 48 hours postoperative. Fatal cases die sooner after the onset of obstruction to-day than they did a century ago.

The treated and the untreated cases of intestinal obstruction present sep-

arate problems, and require separate methods of study. The cause of death in unrelieved cases will be discussed first, and the cause of death in the case which is submitted to operation will be considered subsequently.

I. *Unrelieved Small Intestine Occlusion.*—The animal or man suffering from untreated low small intestine occlusion lives for a period of three or four weeks, during which a number of separate factors combine to produce a gradual deterioration in his general condition and vitality. Each of these morbid factors will be dealt with in turn.

Salt and Water Loss.—In obstruction of the lower ileum, the loss of water and chlorides, while perhaps important in many cases, cannot be held wholly responsible for death. Even in the late stages of the disease, dehydration is often relatively slight (Chart 2), and it is rare to find a reduction of more than 25 per cent in the blood chlorides. In occlusion at higher levels, where chloride loss is the main or sole cause of death, the blood chlorides often reach an agonal level of 50 per cent. Many cases of low small intestine obstruction—the majority of them in my experience—die with no great alteration in the chloride content of the blood, without a high degree of alkalemia, and with little, if any, elevation in the nonprotein nitrogen of the blood. In some cases, no change whatever is demonstrable in the blood chemistry.

Certain cases of low small intestine occlusion do, of course, present a considerable water and salt loss. Vomiting is relatively late, but, above the obstruction, intestinal juices accumulate in the loops of bowel, and distend them so that the veins in the bowel wall are congested, the mucosa becomes edematous, and there is a progressive increase in the secretion of juice from the intestinal glands. Water and electrolytes, accumulating in the lumen of the bowel, are lost to the organism just as surely as if they were immediately vomited. In such cases as these, dehydration and chloride depletion require treatment, and they perhaps play some part in the so-called "toxemia" of obstruction. Yet administration of water and chlorides does not greatly prolong the life of a man or of an animal suffering from unrelieved simple occlusion of the lower ileum.

The duodenal tube, too, invaluable in high intestinal occlusion, has some application in the treatment of low occlusion. Through a nasal suction tube, the duodenal juices may be withdrawn, and may so be prevented from descending into the distended lower loops of bowel and adding to the stagnant intestinal content. The most distended loops of bowel, however, are those which lie immediately above the obstructing agent, and it is difficult, in most cases, to decompress these lower loops satisfactorily by way of a duodenal tube. These lower distended loops appear to be in themselves mainly responsible for the so-called "toxemia" of low small intestine occlusion, and their distention may cause death long before the loss of fluid and salt into them has given rise to any degree of dehydration or hypochloremia. The cause of death in low small intestine obstruction must be sought in the distended bowel loops.

Perforation and Peritonitis.—In the experimental animal, the course of a

low small intestine occlusion is frequently terminated by a perforation of the distended bowel, and peritonitis. This cause of death is not commonly seen now in man, since the patient comes to operation, in the vast majority of cases, before perforation occurs. Reference to any text-book of surgery written during the last century will convince the reader that perforation of the ileum from a stercoral ulcer was relatively common as a terminal event in unrelieved low small intestine occlusion then, just as it is to-day in the experimental animal.[32]

Reflex Nervous Causes.—It has been contended that reflex depression of the circulation by sensory impulses from the distended bowel plays an important part in low intestinal obstruction, but until recently there has been little evidence in favor of this theory. Herrin and Meek[18] succeeded in establishing a distention of bowel without any occlusion of the gastro-intestinal lumen. They isolated a bowel loop and reconstituted the lumen of the intestine around it. The isolated loop was then anastomosed to the reconstituted bowel on the one hand, and brought out on the skin surface on the other. (The fistula produced in this way is known as a Thiry-Vella fistula.) Into this isolated loop a balloon was inserted and inflated. The balloon distended that part of the loop in which it lay, but the bowel on each side of the balloon drained satisfactorily, either into the main intestinal canal or on to the skin surface. Balloon distention of this kind was found by Herrin and Meek to be rapidly fatal, producing a serious diminution of the blood chlorides and elevation of the nonprotein nitrogen. This effect of distention on the blood chemistry Herrin and Meek believe to be due to a reflex hypersecretion of intestinal juice. Denervation of the distended loop permitted the animal to live almost indefinitely. These experiments were repeated by Taylor, Welch, and Harrison,[31] who confirmed the fatal effect of balloon distention of a Thiry-Vella loop, but were not successful in prolonging life by denervation of the distended bowel.

In several experiments, I have maintained balloon distention of Thiry-Vella fistula loops, and have not found that distention, in itself, is necessarily fatal. In one animal, a balloon inserted into a Thiry-Vella loop was maintained at a high state of tension by repeated inflation, yet the animal continued to live, without serious symptoms, for 35 days, when it was sacrificed. During this whole period, the balloon within the fistulous loop was palpable as an abdominal tumor, yet no serious symptoms arose. This single experiment is almost sufficient in itself to suggest that afferent impulses from the obstructed bowel have little, if anything, to do with the so-called "toxemia" of low obstruction.

Splanchnic Congestion.—Loss of blood and plasma into the wall of the distended, congested bowel above a simple occlusion has been said to occasion a depletion of the circulating blood volume, and has been blamed for death in cases of low occlusion. The evidence upon which this theory rests is to be found only in groups of experiments in which the wall of obstructed bowel is weighed, and the amount of fluid and blood lying in it estimated. Actually,

even by this method, when the distended portion of the intestine above the occlusion is compared in weight with collapsed bowel below, the gain in weight of the distended loop from the blood in its congested vessels and the plasma in its edematous wall is relatively small when expressed as a percentage of the blood volume.

TABLE II

LOSS OF EFFECTIVE CIRCULATING BLOOD VOLUME IN SIMPLE LOW SMALL INTESTINE OCCLUSION

Degree of splanchnic congestion measured by a comparison of the weights of loops of equal length taken from above and from below the occlusion after death. (By permission of the Edinburgh Medical Journal)

	Fraction of Intestine Isolated as Closed Loop	Duration of Life	Weight of Closed Loop (Gm.)	Weight of Healthy Loop of Equal Length (Gm.)	Gain in Weight of Closed Loop (Gm.)	Weight of Animal (Gm.)	Blood Volume (approx.) (Cc.)	Loss of Edema Fluid and Blood Expressed as Percentage of Blood Volume
1	One-half....	2 days	48.0	23.0	25.0	3,100	233	11.0
2	One-quarter.	6 days	14.3	9.8	4.5	2,900	218	1.6
3	One-fifth ...	4 days	13.3	10.9	2.4	2,600	195	1.3
4	One-fifth....	4 days	11.1	7.8	3.5	2,400	180	1.8
5	One-fifth ...	3 days	10.9	7.4	3.5	1,900	143	2.5
6	One-seventh	4 days	11.7	7.0	4.7	2,400	185	3.0
7	One-tenth ..	5 days	12.3	8.4	3.9	2,700	203	1.9

TABLE III

LOOPS OF SMALL INTESTINE OF CATS ISOLATED BY DOUBLE LIGATION AND INVAGINATION, AND PERMITTED TO DISTEND AS CLOSED LOOPS

Lengths of bowel equal in length to the closed loops were marked off at the time of establishment of the obstruction by seromuscular stitches of silk; and after the death of the animal were compared in weight with the closed loops. A simple occlusion of the lumen was avoided in these animals by short-circuiting the small intestine around the closed loop.

	Fraction of Small Intestine Distended	Weight of Distended Loop (Gm.)	Weight of Healthy Loop of Equal Length (Gm.)	Weight of Plasma and Blood Lost into Bowel Wall (Gm.)	Estimated Blood Volume (Cc.)	Blood and Plasma Excess in Bowel Wall Expressed as Percentage of Blood Volume
1	One-half.....	105.0	24.0	81	233	34
2	One-half.....	85.0	21.0	64	172	37
3	One-quarter.....	47.4	11.4	36	210	17
4	One-quarter.....	41.0	14.0	27	225	12
5	One-eighth.....	23.5	8.5	15	165	10

In Table II, it will be seen that if an occlusion is established in the middle of the small intestine, the sum of edema-fluid and blood lost into the upper distended half above the obstruction amounts to only 11 per cent of the blood volume. The whole length of small intestine similarly distended would pre-

sumably accommodate a volume of edema-fluid and blood equivalent to little over 20 per cent of the blood volume. Even if this loss were of whole blood, it would be comparable with the blood lost in a considerable, but certainly not in a serious, hemorrhage. The theory of splanchnic congestion, however, has gained so much support, and the measurement of blood lost by the weighing of distended bowel loops is admittedly so inaccurate, that it was felt necessary to estimate directly the effect of splanchnic congestion on the blood volume. In a series of animals, the blood volume was measured on several occasions before the establishment of low occlusion, and at repeated intervals in the survival period after the operation had been performed. Illustrative results are shown in Table IV. Most of the animals died with no alteration whatever in the volume of the whole blood or plasma, and even when death was obviously impending there was no such reduction in blood volume as occurs in extensive strangulation, for example, or in high small intestine obstruction. For this reason, I believe that the loss of blood and plasma into the congested and edematous wall of the obstructed bowel is not the main cause of death in low small intestine occlusion.

TABLE IV

ILLUSTRATIVE DATA FROM DOGS SUBJECTED TO LOW SMALL INTESTINE OCCLUSION

In Dogs Nos. 1 and 4 death has occurred with no reduction whatever in blood volume. In Dogs Nos 2 and 3 there is a considerable reduction in blood volume, in plasma volume, and in cell volume. In these animals, the small intestine was distended to the point of nonviability—a degree of distention-congestion rarely seen in man. (By permission of the British Journal of Surgery)

No. of Exper.	Level of Occlusion	Duration of Life	Mean Blood Volume (Cc.)	Reduction in Blood Volume (Per Cent)	Reduction in Plasma Volume (Per Cent)	Reduction in Cell Volume (Per Cent)
1	Lower ileum.....	14 days	1,170	—	—	—
2	Lower ileum.....	7 days	2,020	23	31	20
3	Lower ileum.....	9 days	1,610	44	50	37
4	Lower ileum.....	9 days	1,410	—	—	—

It is necessary to add, however, that in a certain proportion of animals the blood volume is to some extent depleted before death, and that the depletion affects both plasma volume and cell volume. This occurs only when intestinal distention is extreme, and when the congestion of the bowel wall is so great above the obstruction as to suggest incipient devitalization. Such a marked engorgement of obstructed intestine, frequently seen in the laboratory animal suffering from intestinal occlusion, does not commonly occur now in man. In the untreated case before the days of modern surgery, however, it would appear from the literature that gross congestion of the bowel was common at the time of death, and a considerable blood loss may have been present in these cases, just as it now is sometimes in the experimental animal.

Potassium Poisoning.—Scudder and his coworkers[29] have blamed potassium poisoning for the lethal effects of intestinal obstruction. They have shown that in a certain number of cases the potassium content of the blood is

elevated both in clinical and in experimental cases of intestinal occlusion. Scudder suggests that the elevation of blood potassium is associated with adrenal insufficiency, and recalls that Wohl *et al.*,[37] examining the adrenal glands in obstructed animals, found a depletion of the cells of the cortex. It should be observed, however, that in only seven out of 20 of Scudder's cases was the plasma potassium elevated, and in only five instances was the blood potassium raised. Elevation of potassium, therefore, does not seem to be an essential factor in intestinal obstruction. Scudder found the blood potassium more altered in cases of high occlusion than in cases of low occlusion, and it is noteworthy that Wohl *et al.* observed cortical depletion only in those dogs suffering from intestinal obstruction which were not treated by saline. Saline treatment seems to prevent adrenocortical depletion. It seems possible, therefore, that the alteration in the adrenal glands and in the potassium metabolism may be a function of chloride loss.

It has been shown that adrenocortical extract may be given with benefit in cases of intestinal obstruction, but this is in itself no proof of adrenal deficiency. The beneficent effect of cortical extract may be due purely to the mobilization of chloride which it occasions. It certainly appears to be most effective in cases of high small intestine obstruction where the blood chloride is low.

Toxemia.—From time to time, various toxic theories have been elaborated to explain the lethal effects of intestinal obstruction, the most recent proponent of the toxemia theory being M. J. Bottin,[12] of Liége, who suggests a toxemia of pancreatic origin to explain not only ileal obstruction, but high small intestine obstruction as well. It has never, however, been shown by injection methods that any toxins circulate in the blood of men or of animals suffering from intestinal obstruction, nor, indeed, is this theory of toxemia supported by cross-circulation experiments. This negative statement is no proof, of course, that toxemia does not occur. In an animal suffering from such a definite toxemia as diphtheria or strychnine poisoning, for example, it is difficult to prove, by injecting that animal's blood into another animal of the same size, that the blood has toxic properties. The apparent absence of toxic properties from small quantities, or even large quantities, of blood is no evidence of the absence of toxemia.

There is, however, one important argument against the presence of a toxemia in the patient, or animal, who suffers from intestinal obstruction. That argument is that all absorption is retarded in distended bowel loops. There is no question that many chemical and bacterial toxins are present in the lumen of an obstructed bowel, just as they are present in the lumen of a normal bowel, but in neither case does absorption of that toxic material appear to occur.

Let me recall an important classic experiment of Braun and Boruttau which demonstrates how much absorption is lessened in a distended bowel loop. If, in an experimental animal, a bowel loop is isolated and distended with saline until congestion occurs in the wall of the loop, a fatal dose of strychnine injected into the lumen of the distended loop does not produce any

symptoms of strychnine poisoning. The strychnine has failed to pass from the lumen of the distended loop into the blood stream. A similar retardation of absorption has been shown for electrolytes and for certain dyes.[11, 13, 22] So, in intestinal obstruction, it seems unlikely that there is a passage of toxin from the lumen of the distended bowel to the blood stream.

It might be argued that, though direct absorption from the lumen of the bowel to the blood stream is delayed in the presence of intestinal distention, lymphatic absorption from the distended bowel is accelerated by the congestion which occurs in its wall. Wangensteen[34] has shown experimentally, however, that ligation or division of the lymphatic pedicle draining a distended bowel loop does nothing to prolong life.

Starvation and Alimentary Depletion.—This factor in the morbidity of intestinal obstruction has received insufficient attention. The patient who presents nowadays with low small intestine occlusion has been ill for only a few days, as a rule, and a few days' starvation cannot be responsible then for a fatal issue, though it should be remembered that even a day or two of starvation exaggerates the general effect of any form of trauma or disease. Previously, however, when the patient lived untreated for three weeks or more after the onset of obstruction, starvation must have been an important factor, just as it is, no doubt, in the experimental animal suffering from low small intestine occlusion to-day. In the presence of acute obstruction, the patient or animal, as a rule, refuses food, but even if food materials are ingested they are not absorbed. The intestine above the obstruction is distended, circulation is enormously slowed in the bowel wall, and the main function of the intestine, that of absorption, has come to a standstill. Not only the water and chloride content of the intestinal juice, but the products of digestion, the cholalic acid, the glycine and the taurine of the bile salts, the lipoids (cholesterol and lecithin) of the bile, failed to reach the circulation. The steady loss of these substances over a period of two or three weeks amounts to a serious alimentary depletion.

We have attempted, in the experimental animal, to overcome the factor of alimentary depletion by the intravenous administration of chyle. B. M. Dick[15] first suggested that chyle might prove a suitable food material for intravenous injection in marasmus and other forms of cachexia, and his suggestion has been applied to the treatment of dogs suffering from intestinal obstruction. Large quantities of chyle were collected, and were injected intravenously into obstructed animals.

Technic of Collection of Chyle for Intravenous Administration to an Obstructed Animal.—The difficulty in these experiments was to obtain a sufficient quantity of sterile chyle. It was considered that, by the production of chylothorax in healthy animals, reservoirs of chyle might be obtained, to be tapped at convenient times by paracentesis thoracis. Chylothorax, however, is difficult to produce experimentally. Mouchet[25] succeeded in obtaining chylothorax only twice in a long series of animals, by the establishment of a simple fistula between thoracic duct and pleural cavity, and even in these two cases the chylothorax was transitory.

In our earlier experiments, it was found that if the thoracic duct is merely

divided and its lower end transplanted into the pleural cavity, the communication between duct and pleura rapidly closes. Apparently, after division of the thoracic duct, other anastomotic lymphatic channels open, and a new route is established for the passage of chyle from the abdomen to the great veins of the neck. It was felt that, in addition to an anastomosis between thoracic duct and pleura, some means must be found of preventing chyle from reaching the great veins by alternative routes. The simplest method of interfering with the drainage of chyle into the veins of the neck appeared to be by the ligation of the superior vena cava. Ligation of the left innominate vein did not suffice to produce an actual stasis, since, in the dog at least, there appears to be a subsidiary route for chyle by way of the right lymph duct to the right innominate vein. The following method was, therefore, elaborated. The right pleural cavity was opened, and the thoracic duct identified in the lower mediastinum. The mediastinal pleura was then torn through with an aneurysm needle, and the thoracic duct cut across. The superior vena cava was then ligated in the upper part of the mediastinum, and the vena azygos was also ligated toward its termination. After this operation, a chylothorax developed on the right side in nearly every case. The pleural cavity was tapped daily after the operation. On the first few occasions, a thin, blood stained fluid was withdrawn, but, later, white, milky chyle was obtained. Sometimes as much as 500 cc. of chyle was obtained daily from the larger dogs. The chyle obtained in this way clotted soon after withdrawal if left at room temperature, and the addition of citrate did not, of course, prevent coagulation. It was found, however, that if the chyle was placed in a refrigerator immediately after withdrawal, coagulation was largely avoided. Our routine practice, therefore, was either to inject the chyle obtained immediately, or, better, to leave the chyle at a refrigerator temperature of 1° or 2° F. for a day or two. Before injection, any coagulum was removed by filtration.

In this way, a constant reservoir of chyle was available. A number of animals were subjected to low small intestine occlusion, and were treated by the daily intravenous injection of chyle. It was found that in no case did the chyle exercise an obvious toxic effect. The average daily dose of chyle was arbitrarily fixed at 30 per cent of the estimated blood volume of the recipient dog. Five dogs were treated in this way. One of these died after a period of ten days. Two other dogs lived for a period of three weeks. One dog lived until the thirty-first day, and in the fifth animal, death was postponed till the thirty-fifth day. All five animals died of perforation of the small intestine, and peritonitis. The statistics in this series are not, of course, conclusive; suggestive as they are, they are best left without comment. They perhaps indicate, however, that the transfusion of chyle as a treatment of alimentary depletion and starvation might prove a fruitful field for investigation.

II. *The Cause of Death in Cases of Low Small Intestine Occlusion after Operative Relief of the Obstruction.*—It has already been mentioned that no definite toxemia has ever been proved to be present during the actual presence of an abdominal distention or obstruction. There is, however, some evidence

that a toxemia may result from the sudden deflation of distended bowel loops. We are all familiar with the clinical case of intestinal obstruction in which the patient is admitted to hospital relatively early in the disease, with a considerable abdominal distention, but yet in a fairly good general condition. Operation is performed, and the obstruction is successfully relieved. After operation, the abdomen loses its distention to some extent, yet the patient gradually sinks into a listless apathy, the pulse rate rises, the blood pressure falls, and in an hour or two, or in a day or two, the patient dies. The patients who die from intestinal obstruction nowadays die, as a rule, after an operation has been performed.

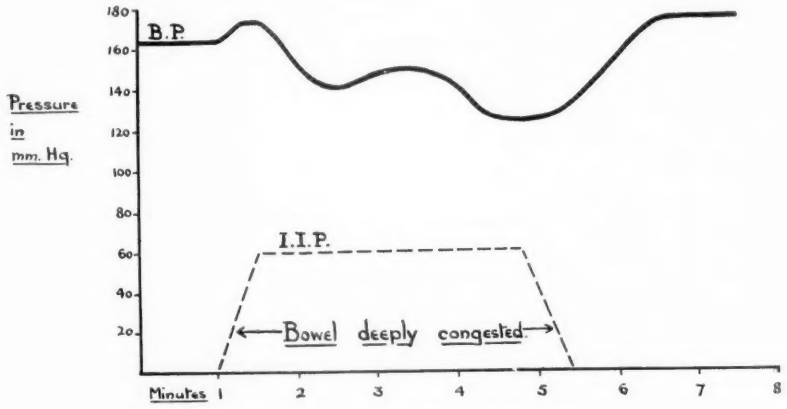


CHART 3.—Demonstrating that induction of distention and congestion of small intestine causes a fall in systolic pressure, apparently the result of splanchnic congestion. Relief of distention and congestion after a few minutes is followed by elevation of systolic pressure, as a result of the return of blood from the congested bowel to the general circulation. (Cf. Charts 4, 5 and 6.)

The same phenomenon is seen clinically in an even more extreme degree in cases where a strangulation is relieved by operation, and it is seen in its most characteristic form after reduction of an intussusception. There are cases of intussusception in which, at operation, the intussusception is reduced, and the intussusceptum, obviously still viable, is returned to the abdomen; after operation, within 24 hours, as a rule, the temperature and the pulse rate rise, the systolic blood pressure falls, the patient becomes pale, sometimes listless, sometimes excited, and death may occur. This alarming phenomenon sometimes happens rapidly, and it may even occur on the operating table. It is notorious that the postoperative course of an intussusception is likely to be more serious if the invagination is difficult to reduce, and if the intussusceptum has to be forcibly squeezed out from its sheath by a long-continued manipulation.

The rapid and lethal depression of the systolic blood pressure which may

follow relief of an intestinal obstruction was seen with greater frequency in former times, when attempts were made by aspiration of distended bowel loops to empty these loops rapidly at operation, and when it was customary to milk down distended bowel at operation, to evacuate it. Let us examine whether the postoperative deaths in intestinal obstruction are due simply to the

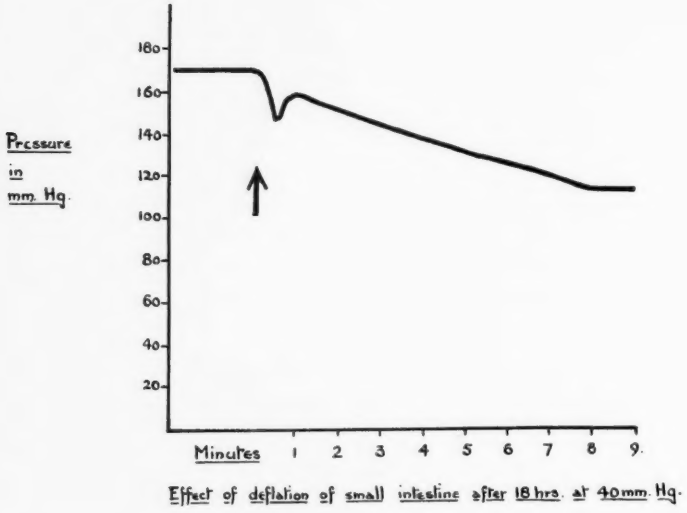


CHART 4.

CHARTS 4, 5 and 6.—Demonstrating that release of a long-continued distention-congestion of bowel in the dog is followed by a serious, and sometimes fatal, depression of the systolic pressure.

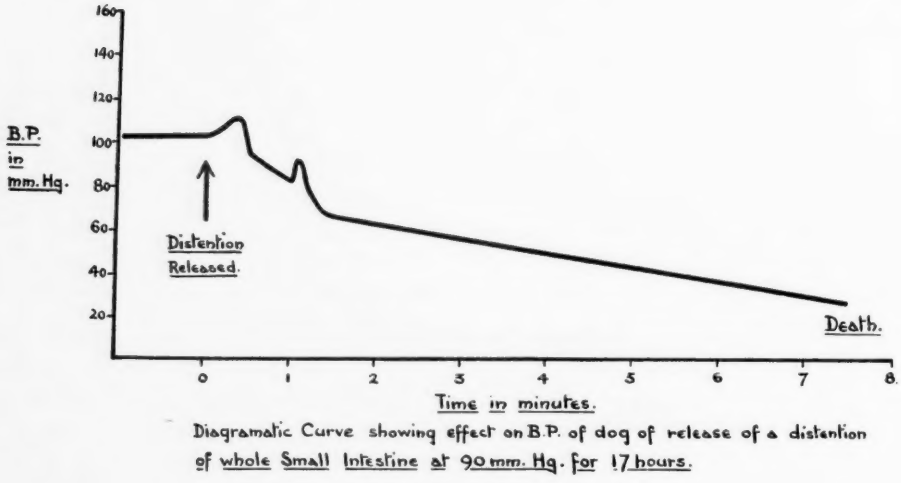


CHART 5.

shock of an abdominal operation performed upon a seriously ill patient, or whether there is a specific depressor factor in the actual release of obstruction.

It has been possible, experimentally, to produce a depressor effect in ani-

mals by the sudden relief of intestinal distention.[2, 3, 4] If the whole small intestine of an animal is rapidly inflated to the point of cyanosis, there is a sudden depression of the systolic blood pressure. This appears to be due to the loss of effective circulating blood into the distended vessels of the inflated bowel, and is an effect of splanchnic congestion; after its initial depression, the blood pressure usually rises again quite rapidly to normal. If the distended bowel is suddenly collapsed soon after its inflation, its congestion quickly disappears, its engorged veins empty, there is an increased blood return to the heart, an augmentation of the circulating blood volume, and a transient rise in blood pressure (Chart 3). If, however, the intestinal distention is maintained for a long period, and is then rapidly released, there occurs, not an elevation, but a depression of the blood pressure (Charts 4, 5, 6 and Table V).

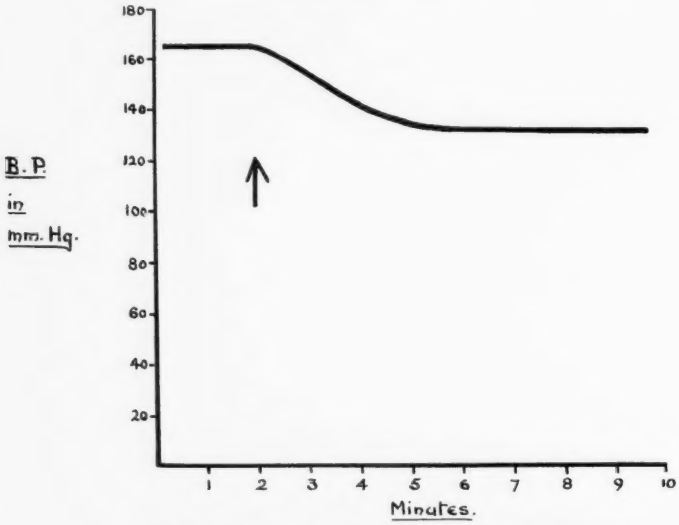
TABLE V

EXPERIMENTS SHOWING EFFECT OF RELEASE OF DISTENTION-CONGESTION OF BOWEL

Early relief leads to increased return of venous blood from congested bowel to heart. Systolic pressure rises (protocols Nos. 1 to 9). The delayed relief of long-continued distention-congestion is followed by improvement in color of bowel, presumably by increased blood return to the heart, but by a depression instead of an elevation of the systolic pressure. This suggests the return of a depressor substance to the general circulation from the previously obstructed intestine (Exper. Nos. 10 to 14).

No. of Exper.	Intra-intestinal Pressure Induced	Animal	Afferent Paths from Heart Interrupted	Afferent Paths from Intestine Interrupted	Duration of Distention	Change in Bowel Circulation (color)	Alteration in B.P.	Explanation
1	62 Mm.Hg.	Dog	Yes	No	5 min.	Return from cyanosis to normal	+ 28	
2	80 "	Cat	Yes	No	5 min.	"	+ 50	Increased
3	90 "	Dog	Yes	Yes	2 min.	"	+ 30	
4	90 "	Cat	Yes	Yes	5 min.	"	+102	return of
5	100 "	Dog	Yes	Yes	4 hrs.	"	+ 28	
6	120 "	Dog	Yes	Yes	8 hrs.	"	+ 44	venous
7	90 "	Dog	Yes	Yes	7 hrs.	"	+ 22	
8	80 "	Cat	Yes	Yes	5 hrs.	"	+ 68	blood to
9	Release of ligation of superior mesenteric vein of dog					"	+ 24	heart
10	90 Mm.Hg.	Dog	Yes	Yes	6 hrs.	Return from cyanosis to normal	− 55	? Return of depressor substance
11	90 "	Dog	Yes	Yes	17 hrs.	"	− 78 (death)	in blood from intes-
12	90 "	Dog	Yes	Yes	18 hrs.	"	− 32	tine
13	40 "	Dog	Yes	Yes	12 hrs.	"	− 56	
14	80 "	Dog	No	No	12 hrs.	"	− 23	
15	90 "	Dog	Yes	Yes	21 hrs.	Remained cyanosed	No change	Thrombosis in bowel
16	90 "	Dog	Yes	Yes	17 hrs.	"	"	veins

The fall in blood pressure in these animals occurred even after the complete denervation of the bowel, either by division of the mesenteric nerves or by bilateral excision of the sympathetic trunk and double vagotomy. When the distended intestine is deflated, the distended intestinal veins empty, blood returns from these veins to the general circulation and augments the blood volume, and yet, instead of a rise of blood pressure, there is a fall, which is sometimes progressive over a period of some hours, and which is occasionally fatal. This fall in blood pressure would appear to be due to the passage of toxic depressor material into the blood stream. Toxic material from the lumen has, during distention, diffused into the tissue fluids of the bowel wall, but has failed to enter the blood stream, because of the intestinal congestion which is



Dog. Effect of sudden release (at arrow) of an intraintestinal pressure of 90 mm. maintained for 18 hours.

CHART 6.

present. On the relief of congestion, the tissue fluid, bearing the toxic material which it has acquired during distention, enters the intestinal capillaries and returns with the intestinal blood to the general circulation, to exercise a depressor effect.

Braun and Boruttau recorded an ingenious and dramatic experiment which is of some value in this connection. As I have already mentioned above, Braun and Boruttau found that a lethal dose of strychnine could be injected into an isolated and distended bowel loop in the experimental animal without the appearance of symptoms, provided the intra-intestinal pressure was sufficiently high in the isolated loop. They showed, however, that sudden deflation of the strychnine-containing loop was followed, as a rule, by the immediate appearance of strychnine convulsions, and by the early death of the animal. The effects of sudden deflation of a distended loop containing strychnine were

almost as rapid as the effects of intravenous injection of the drug. Braun and Boruttau explain these experiments in this way: They consider that, during distention, the strychnine passes into the stagnant tissue fluid of the congested wall of the distended bowel, but fails to pass into the blood stream, because of the sluggishness of local circulation in the bowel. As soon as the distention and congestion of the bowel loop are relieved, however, the local circulation recovers, and strychnine is able now to diffuse rapidly from the tissue spaces into the blood stream. It appears likely that, in intestinal obstruction, toxic material from the lumen behaves in the same way. During distention it passes into the tissue spaces of the bowel wall, but succeeds in reaching the blood stream only when the local circulation in the bowel is improved by deflation.

The nature of the toxin which produces a depressor, and sometimes a lethal, effect on the experimental animal after the relief of an obstruction is not known. Blood collected from the portal vein and from the mesenteric veins during deflation of a distended bowel loop has been shown to have sometimes a depressor effect when injected into other animals.[4] It can thus be fairly argued that, while no proof has ever been offered of a true toxemia during intestinal distention, there is considerable evidence that a rapid toxemia may occur soon after the relief of intestinal distention.

One important principle emerges—the immediate relief of an early obstruction is beneficial—a low blood pressure will rise. Sudden release of a long-continued distention of the bowel, with severe intestinal cyanosis, is likely to be followed by a perhaps dangerous fall in blood pressure, and some part of the present (postoperative) mortality of obstruction may be explained by the depressor effect of sudden relief of intestinal distention-congestion.

The results of sudden intestinal deflation are an important argument against aspiration of distended bowel loops at operation, and the milking down of distended bowel to empty it forcibly; Storck and Ochsner[30] have demonstrated how serious a depressor effect such mechanical decompression of the intestine may have on the carotid blood pressure in the experimental animal.

The depressor effect of deflation in the experimental animal may suggest that any form of relief of a long-continued obstruction may not be without danger. The risk of sudden decompression of distended bowel has been particularly stressed by Wheeler,[35] who points out that wherever fluid is present under tension in the body a sudden evacuation of the fluid may have a serious effect; Wheeler advocates that distended bowel in obstruction be decompressed as slowly as the pleural cavity in empyema, or the distended bladder in retention of urine. Our experiments in deflation of bowel strongly support Wheeler's contention. The surgeon who accepts the validity of our argument is on the horns of a dilemma when faced with an acute intestinal obstruction of long standing. On the one hand, he cannot permit obstruction to continue, and on the other, he is aware of the possible risk of sudden release of the obstruction. Time alone will produce a satisfactory solution of this problem. In the meantime, the experiments described strongly support recent suggestions for slow decompression of distended bowel, either by preoperative nasal

suction drainage, as suggested by Wangensteen,[34] or by some form of controlled enterostomy which permits the distending gas to escape, only gradually, over a period of some hours.

Let it be understood, finally, that this demonstration of a toxemia which follows upon the sudden relief of a long-continued intestinal distention can be applied only to the postoperative toxemia of acute intestinal obstruction. There is no evidence that an actual toxemia is present during the presence of an unrelieved intestinal distention. It might be argued that, during distention, a sudden wave of peristalsis passing over the distended bowel might squeeze from it, into the circulation, some of the toxic products which appear to lie within its wall. Peristalsis may perhaps have the same effect during an obstruction as do milking and stripping of the bowel at the time of operation. A theory of an intermittent toxemia due to the entry into the circulation of toxic material from the bowel with each vigorous peristaltic wave must remain a matter of conjecture. The other morbid factors which have been shown to be present throughout the relatively long course of an untreated low small intestine obstruction are sufficient, however, to explain death, and there need be no resort to a hypothetic, intermittent toxemia in these cases.

(3) *Colonic Occlusion.*—Colonic occlusion is particularly well tolerated in experimental animals, and dogs with a complete obstruction of the lower colon may live without symptoms for as long as a month. This is hardly comparable, however, with colonic occlusion as it occurs, typically, in man. The cause in man is usually cancer, and acute obstruction, when it supervenes, occurs only as the culmination of a long-continued, subacute obstruction, as a rule. The bowel has already been dilated, its muscle wall hypertrophied, and the mucosa not infrequently the seat of stercoral ulceration before obstruction becomes complete. Furthermore, the patient is frequently in poor general condition, and sometimes even cachectic. For this reason, colonic occlusion is a more serious form of obstruction in man than it is in the experimental animal. If the occlusion becomes complete, the intracolonic pressure rises to a high level, but the ileocecal sphincter remains competent until a late stage. Ultimately, in most untreated cases, the pressure rises to such a high level within the colon that perforation of its wall occurs, the perforation being situated, as a rule, in a stercoral ulcer of the cecum. In most cases of colonic occlusion, no significant alteration occurs in the blood chlorides, the blood volume, the bicarbonate content, or the blood urea.

B. CLOSED LOOP OBSTRUCTION

Closed loop obstruction has specially lent itself to experimental study, and, as Wilkie first observed, the pathologic course of a closed intestinal loop depends upon the degree to which its contents are infected by bacteria.

(1) *Loops with Sterile Content.*—The best examples of the sterile loop in man are mucocele of the appendix, cyst of the vitello-intestinal duct, and the various enterogenous cysts. As a rule, when a sterile loop of bowel is isolated from the intestinal tract, it dilates gradually with mucus, and no general effects

follow. In the experimental animal, an isolated bowel loop can be effectively sterilized, and, in most cases, after its ends are closed, it dilates, as a similar loop does in man—as a mucocele. In only a few cases does the loop distend so rapidly with mucus that vascular changes occur in its wall, and the animals die after three or four days (Taylor[31]).

(2) *Closed Loops with Heavily Infected Content.*—Wilkie's[36] second form of closed loop obstruction is best seen clinically in obstructive appendicitis. Such a loop contains grossly infected fecal matter, and is closed at both its ends. The organisms within it multiply rapidly, gas accumulates in the lumen, the pressure within the loop rises rapidly, fluids and leukocytes are poured into the lumen, and a pyocele, or empyema, forms. Soon the increase in pressure interferes with the local circulation, organisms enter the devitalized bowel wall, and gangrene, perforation and peritonitis follow. Other things being equal, a small infected loop is more liable to early perforation than is a long one, perhaps because a small loop accommodates itself less easily to a rapid increase in the volume of its content, and more rapidly develops a high pressure within it.

(3) *Closed Loops with Mildly Infected Content.*—Loops of this sort are seen between multiple strictures of the small intestine and in herniae which are obstructed but not yet strangulated. In the clinical case in man, a closed loop is always complicated by a simple bowel occlusion above it, but in the experimental animal closed loops can be prepared without a complicating occlusion. The closed loop is in that case short-circuited by anastomosis, and is sometimes employed in the study of the so-called "toxemia" of obstruction. The closed loop distends in the course of a few days with foul gas and with dark-brown, blood stained fluid, whose constituents include intestinal juice, leukocytes, fragments of dead epithelium, whole blood and bacteria. The intraloop tension reaches an enormous level, sometimes as high as 70 cm. of water, because the closed loop cannot relieve the pressure within it by evacuation of some part of its content upwards, as the distended bowel above a simple occlusion can. The intra-intestinal pressure within a closed loop rises more rapidly and to a higher level than does the pressure in the bowel loops above a simple occlusion. The walls of the loop are tense and congested and edematous, with bacterial invasion and leukocyte infiltration. The mucosa is necrotic and ulcerated, as a result of the high tension within the loop, and cyanosis is soon obvious in it. The muscle coat is flabby and inflamed, and the serosa is usually congested. The terminal changes in the bowel wall are sometimes very similar to the changes of strangulation.

A loop of this kind closely resembles the lowest distended loop above a simple low intestine occlusion, and it is difficult not to believe that the cause of death is similar in both these conditions. There are certain modifying factors, however, in the course of a closed loop: Perforation and peritonitis, while not necessarily present before death, are rather more frequent in the closed loops than in cases of simple occlusion. Where death occurs without perforation and peritonitis, the closed loop will usually be found in a state of gross conges-

tion, and reference to Table III will demonstrate that the blood and fluid lost into the wall of a long, closed loop may amount to as much as one-third of the total blood volume. So great, indeed, may be the congestion of the loop that at the time of death it may be considered to be in a state of strangulation, not from occlusion of its mesenteric vessels, but from closure of the vessels in the wall of the loop itself, as a result of the enormous intraloop pressure. The relatively common incidence of perforation and peritonitis, the increased degree of blood loss from the general circulation, and the occurrence of actual devitalization in the wall of the distended bowel are three factors which explain why the course of closed loop obstruction is so much more rapid than the course of simple occlusion of the bowel.

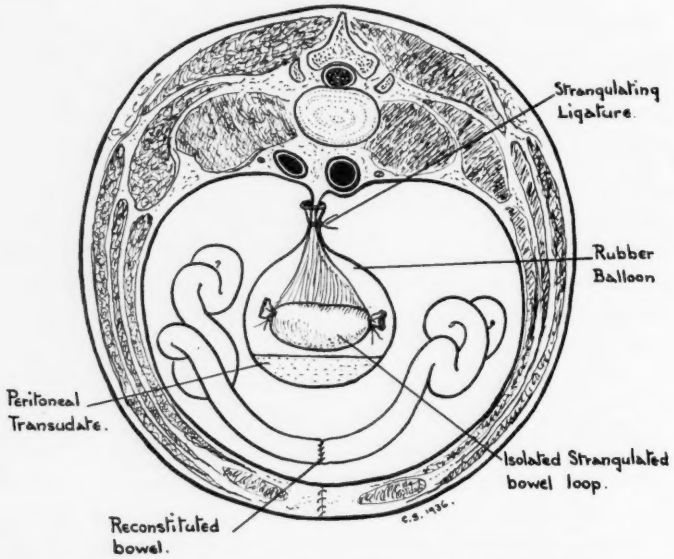


FIG. 1.—Showing the method of determining blood loss following strangulation (Foster and Hausler). An isolated bowel loop is placed in a rubber bag, and strangulated by a ligature tied around the neck of the bag. The intestinal lumen is reconstituted around the isolated loop by anastomosis.

It should be remembered that sudden deflation of a closed loop may exercise the same toxic effect as sudden relief of a simple occlusion or a strangulation.

C. INTESTINAL STRANGULATION

Pure forms of intestinal strangulation are rare clinically. In strangulation by hernia, for example, or by a band, a simple occlusion is present usually above the strangulated loop, but the effects of strangulation are so rapid, as compared with the effects of simple occlusion, that the strangulation element always outweighs in importance the occlusive element. Strangulation is seen in a pure form in mesenteric embolism and thrombosis.

It is convenient to consider strangulation under three heads, since the predominant lethal factor appears to vary according as a strangulated loop is very short, very long, or of medium size.

(1) *Short Loop Strangulation.*—This form is exemplified clinically by the small, nonviable patch of bowel wall which, on occasion, may occur in a Richter's hernia, or at the apex of a reduced intussusception. It is also seen clinically in the late obstructed appendix when circulation has ceased in the vessels of the appendix wall. In strangulation of a short loop, death is due, as a rule, to gangrene, rupture and peritonitis.

(2) *Long Loop Strangulation.*—Long loop strangulation is clinically exemplified by mesenteric thrombosis and embolism, and the picture of the patient suffering from occlusion of the superior mesenteric artery or vein is characteristic. The sudden pain at the onset of the disease is followed rapidly by a progressive pallor, increase in pulse rate, and fall in blood pressure. An enormous volume of blood is lost into the bowel lumen, into the peritoneal cavity, and into the congested wall of the bowel itself, and the patient dies after a few hours just as he would die from a massive internal hemorrhage. The amount of blood lost by the experimental animal in an extensive strangulation has been measured by Holt[19] and by Scott and Wangensteen.[27] The strangulated loop is surrounded by a rubber bag (Fig. 1), and the amount of blood lost is the sum of the blood in the lumen of the bowel, the blood in the rubber bag around it, and the blood lying in the congested vessels and tissue spaces of the bowel wall itself. The actual amount of blood lost into the lumen and the rubber bag is estimated by the measurement of the hemoglobin content of the fluid in these two situations. The blood lost into the intestinal wall is measured by the increase in weight of the strangulated loop at the time of death. Scott and Wangensteen decided from their experiments that 66 per cent of the total blood volume could be lost in this way. Holt,[19] using a similar technic, estimated the blood loss at 50 per cent in certain cases, and my experiments support these statistics. The estimations of blood loss obtained in my rubber bag experiments[6] are shown in Table VI.

It has been argued that the rubber bag technic, which was first introduced by Foster and Hausler,[17] gives a false estimate of the amount of blood lost in this condition, since, in strangulation in man, a proportion of the lost volume is reabsorbed by the peritoneum. I have attempted to measure the blood volume directly, however, in animals suffering from massive strangulation,[7] and have found that the diminution of blood volume after the production of massive strangulation is dramatic (Table VII). When the whole small intestine of an animal is strangulated, there is a reduction of approximately 50 per cent in the blood volume of the animal when death occurs a few hours after the strangulation is induced. The reduction affects the cell volume to a much greater extent than the plasma volume, since, even during the short period of progressive blood loss, an attempt is made to maintain the blood volume by the passage of tissue fluids into the circulation (Chart 7). The effect of massive venous strangulation on blood volume is precisely similar to the effect of a rapid hemorrhage. The clinical application of these experiments is important. The patient suffering from massive strangulation requires blood transfusion, and not the introduction of a mere pint of blood, but the addition from donors

TABLE VI

SHOWING THE AMOUNT OF BLOOD APPARENTLY LOST INTO A STRANGULATED LOOP SURROUNDED BY A RUBBER BALLOON

The loss of one-third of the blood volume by hemorrhage is serious, and loss of one-half of the blood volume by hemorrhage is likely to be fatal. (By permission of the Edinburgh Medical Journal)

No. of Exper.	Fraction of Jejuno-Ileum Strangulated	Weight of Balloon plus Content (Gm.)	Weight of Balloon plus Normal Loop of Equal Length (Gm.)	Weight of Blood Lost (Gm.)	Estimated Blood Volume (Cc.)	Blood Loss as Percentage of Whole Blood Volume	Duration of Life
1	One-half.....	170	60	110	210	52	Died in 24 hrs.
2	One-half.....	220	140	80	188	43	Died in 24 hrs.
3	Two-sevenths.	132	90	42	120	35	Killed after 18 hrs.
4	One-quarter..	193	154	39	172	23	Killed after 24 hrs.
5	Two-ninths...	184	142	42	158	27	Killed after 18 hrs.
6	Two-ninths...	160	107	53	165	32	Killed after 18 hrs.
7	One-fifth.....	142	111	31	135	23	Killed after 18 hrs.
8	One-fifth.....	203	151	52	188	28	Killed after 24 hrs.
9	One-seventh..	173	140	33	150	22	Died after 20 hrs.

TABLE VII

VENOUS STRANGULATION

EFFECT OF STRANGULATION ON THE BLOOD VOLUME, PLASMA VOLUME AND CELL VOLUME

It will be seen that in the longer strangulations the blood volume may be reduced to approximately one-half of its normal level. The cell volume is proportionately more reduced in most cases than the blood volume, as there is an attempt at replacement of the lost blood by the passage of tissue fluids into the circulation, just as after a rapid hemorrhage. In short strangulations, the plasma loss exceeds the blood loss; these animals live for a relatively long period, and suffer severely from vomiting before death.

No. of Exper.	Amount of Small Intestine Strangulated	Duration of Life	Mean Blood Volume (Cc.)	No. of Preoperative Readings	Reduction in Blood Volume	Reduction in Plasma Volume	Reduction in Cell Volume
1	Whole length.....	7¼ hrs.	870 ± 16%	9	44%	37%	47%
2	Whole length.....	2½ hrs.	430 ± 8%	9	52%	50%	59%
3	One-third.....	12 hrs.	740 ± 9%	7	30%	16%	50%
4	One-third.....	5 hrs.	1,170 ± 10%	5	49%	30%	66%
5	One-fifth	5 hrs.	1,240 ± 4%	10	40%	30%	55%
6	One-third.....	5½ hrs.	1,480 ± 7%	7	43%	27%	68%
7	One-tenth (approx.).	24 hrs.	1,060 ± 9%	5	17%	30%	8%
8	One-twentieth (approx.).....	4 days	2,150 ± 2%	5	15%	21%	10%
9	One-fortieth (approx.).....	12 days	1,570 ± 11%	8	Nil	Nil	Nil

of an amount of blood equivalent to almost one-half of the patient's blood volume. Massive strangulation, extensive mesenteric thrombosis, for example,

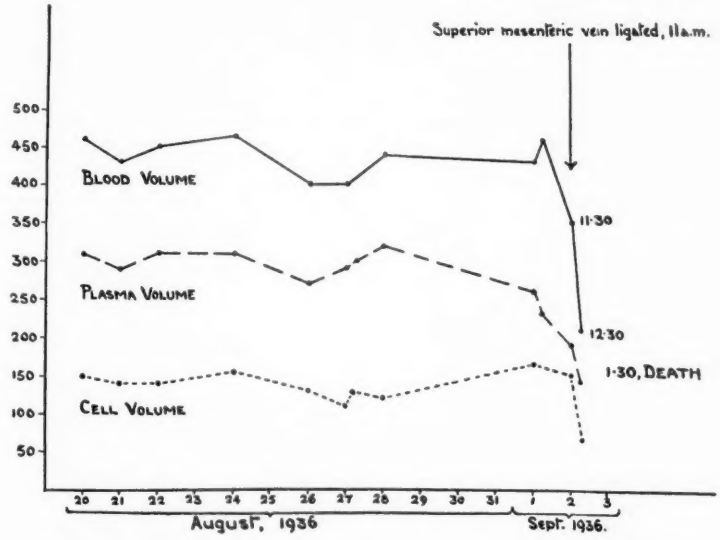


CHART 7.—Dog. Weight 6.8 Kg. Massive venous strangulation: Death in two and one-half hours. Blood volume reduced by 52 per cent, cell volume by 59 per cent, at time of death. (By permission of the British Journal of Surgery)

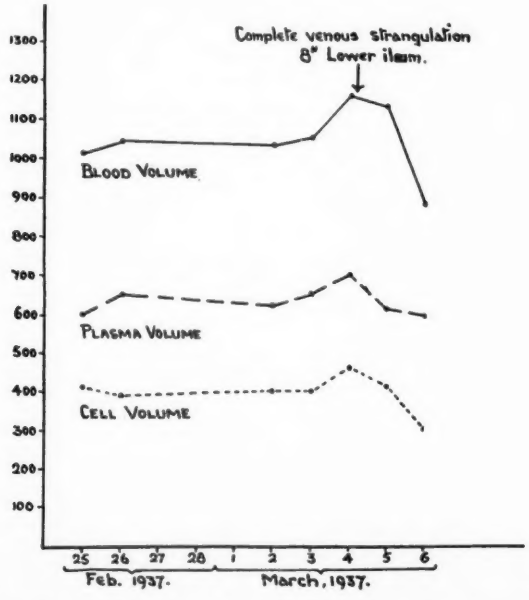


CHART 8.—Dog. Weight 17.5 Kg. Medium loop strangulation: Slight terminal reduction in blood volume, insufficient to be responsible for death. (By permission of the British Journal of Surgery)

requires massive transfusion, and operation is justifiable only after the blood volume has been restored to an approximately normal level.

(3) *Strangulation of Loops of Medium Length.*—Blood loss from the general circulation, while sometimes considerable in this form of strangulation, is not sufficiently great to account for death. The effect on the blood volume is not, as a rule, remarkable. In an animal suffering from strangulation of one-fortieth of its small intestine, there was no alteration in the blood volume, in the plasma volume, or the cell volume, at the time of death. In an animal with one-twentieth of the small intestine strangulated, there was a 15 per cent reduction in blood volume; in an animal with one-tenth of its small intestine strangulated a reduction of 17 per cent in the blood volume at the time of death (Chart 8), and the cell reduction in these cases was inconsiderable, the great part of the depletion of blood volume being due to a loss of plasma (Table VII).

Foster and Hausler[17] first showed that the cause of death in medium loop strangulation is the absorption by the peritoneum of toxic material which has its origin in the strangulated loop. If a loop of small intestine of medium length is isolated, and intestinal continuity reestablished by anastomosis, and if the isolated loop is now surrounded by a rubber bag and strangulated by a ligature tied around the neck of the bag where it encircles the mesentery of the isolated loop, the experimental animal may survive indefinitely (Fig. 1). Foster and Hausler showed, further, that the blood stained transudate which collects in the rubber bag, and which, in the absence of the bag, would be absorbed by the peritoneum, has a toxic effect when injected into other animals. Holt[19] also made an extensive study of the toxicity of the peritoneal transudate from strangulated loops of medium length, and came to the conclusion that two separate toxic elements were present—one which passed outwards from the loop almost immediately after the establishment of strangulation, and which he considered a product of abnormal tissue metabolism; the other a late addition to the transudate, and apparently bacterial in origin. If a chemical fractionation is performed of the transudate collected in one of Foster and Hausler's rubber bags, it is found that two of the chemical constituents of the transudate appear to exercise a toxic effect. One of these is contained in the diffusible fraction of the transudate, while the other is precipitated with the euglobulins. The transudate exercises a considerable depressor effect on the blood pressure when injected intravenously in any anesthetized animal, and attempts have been made to identify the depressor substance concerned.[3, 9, 19, 23, 33] Early measurements of the histamine content of the transudate by biologic assay suggested that a high proportion of histamine was present in the transudate from strangulated loops, and the total histamine content of the transudate from an eight-inch strangulated loop in a cat was considered then to amount to as much as 4 mg. in some cases. High as this concentration appeared to be, it did not entitle histamine to be regarded as the sole lethal factor, or, indeed, as an important lethal factor, in intestinal strangulation, for the gradual absorption by the peritoneal cavity of 4 mg. over a period of 24 hours would exercise no effect on the animal concerned. Maycock,[23] with a more recent technic of histamine assay, estimated the histamine content of the fluid collected from nonviable strangulated loops to be from 0.3

to 2.0 gamma per cc., with a maximum total of one-sixth of a milligram in the whole amount of fluid collected; he further estimated the choline percentage at from 8 to 75 gamma per cc. of fluid. Maycock concluded that these amounts of histamine and of choline were sufficient to explain the depressor effect of the peritoneal fluid collected from strangulated intestine, but were not sufficient to account for death in that condition. He tended to minimize the importance of a toxic element in the peritoneal transudate. He found that the slow intravenous infusion of peritoneal transudate into normal anesthetized animals has usually no depressor effect upon the blood pressure, although in six out of ten of Maycock's experiments the animal into which the transudate was poured died. Maycock was disinclined to believe that the toxicity of the peritoneal transudate, even in association with the serious depletion of blood volume which sometimes occurs in these animals, was responsible for death in intestinal strangulation. His grounds for this view were that in ten cats, in whom strangulation transudate was injected intraperitoneally after removal of from 51 to 73 cc. of blood, only three cats died, and the remaining cats appeared to be unaffected. It seems clear from Maycock's experiments that the histamine and choline content of peritoneal fluid is not of sufficient amount to be an important lethal factor in strangulation, yet the toxicity of this fluid is well established, and appears to lie, as I have said, partly in the diffusible fraction, partly in the euglobulin fraction of the transudate.

The toxicity of the transudate appears to depend upon the presence of bacteria within the strangulated loops. Closed loops of dead sterile bowel taken from newborn guinea-pigs, a few hours after birth, and transplanted into the peritoneal cavities of other animals, disappear without trace and without injury to the host (Table VIII). Dead, closed loops from older guinea-pigs, similarly transplanted, contain both aerobic and anaerobic organisms, and lead to the death of their hosts within a few hours, without peritonitis. The recipient animals die in these circumstances because of the nonviability of the transplanted loop, in combination with the bacteria which it contains.[4]

TABLE VIII

EFFECT OF TRANSPLANTATION OF BOWEL FROM NEWBORN GUINEA-PIG INTO CAT

In Expers. 1, 2 and 3, the transplanted small intestine is sterile, and disappears in the peritoneal cavity of the host without trace and without effect. In Expers. 4 and 5, the host died—without peritonitis, but apparently from the absorption of toxins from the dead transplanted and infected loop of older guinea-pigs.

No. of Exper.	Age of Guinea-Pig Donor	Culture of Content of Guinea-Pig Bowel	Effect of Transplant on Cat Host
1	8 hrs.	Sterile	No ill effects: Indefinite survival
2	32 hrs.	Sterile	No ill effects: Indefinite survival
3	56 hrs.	Sterile	No ill effects: Indefinite survival
4	72 hrs.	Aerobes and anaerobes	Died 24 hrs. Transplanted bowel distended. No peritonitis
5	96 hrs.	Aerobes and anaerobes	Died 20 hrs. Transplanted bowel distended. No peritonitis

TABLE IX

RELATION OF BACTERIA TO THE TOXICITY OF THE PERITONEAL TRANSUDATE IN STRANGULATION

Development of toxicity in peritoneal transudate from strangulated loops. Transudate from early strangulations is nontoxic; and the seromuscular coat from the strangulated bowel in these is sterile. Transudate from later strangulated loops is toxic, and the outer coats of the strangulated bowel, though not necessarily the transudate itself, are infected.

Length of Bowel Strangulated	Length of Survival Period	Results of Intraperitoneal Injection of Balloon Fluid	Cultures of Seromuscular Coat	Cultures of Balloon Fluid
Whole small intestine	Died in 6 hrs.	Whole amount nontoxic to guinea-pig	Sterile	Sterile
1 foot ileum	Killed in 8 hrs.	"	Sterile	Sterile
1 foot jejunum	Killed in 10 hrs.	"	Sterile	Sterile
1 foot ileum	Killed in 12 hrs.	"	Sterile	Sterile
1 foot jejunum	Killed in 15 hrs.	"	Sterile	Sterile
1 foot ileum	Killed in 18 hrs.	"	Sterile	Sterile
1 foot jejunum	Killed in 18 hrs.	"	Sterile	Sterile
1 foot ileum	Killed in 18 hrs.	"	Sterile	Sterile
2½ feet jejunoileum	Died in 24 hrs.	"	Sterile	Sterile
1 foot jejunum	Killed in 30 hrs.	Whole amount killed cat in 8 hrs. [1, 2, 3, 5]	Aerobes and anaerobes	Aerobes and anaerobes
1 foot ileum	Killed in 18 hrs.	5 cc. killed g.-p. in 8 hrs.[1, 2, 3, 4] 2 cc. killed mouse in 2 hrs.	Aerobes and anaerobes	Sterile
2½ feet jejunoileum	Died in 24 hrs.	2 cc. killed g.-p. in 4 hrs.[1]	Aerobes and anaerobes	Aerobes and anaerobes
1 foot ileum	Killed in 24 hrs.	5 cc. killed g.-p. in 7 hrs. [1, 2, 3]	Aerobes and anaerobes	Aerobes and anaerobes
9 inches ileum	Died in 20 hrs.	5 cc. killed g.-p. in 6 hrs.[1, 2, 5] 2 cc. killed mouse in 2 hrs.	Aerobes and anaerobes	Aerobes and anaerobes
1 foot ileum	Killed in 24 hrs.	5 cc. killed g.-p. in 8 hrs.[1, 2, 3, 4]	Aerobes and anaerobes	Aerobes and anaerobes
1 foot ileum	Killed in 20 hrs.	5 cc. killed g.-p. in 6 hrs.[1, 2]	Aerobes and anaerobes	Sterile
1 foot ileum	Killed in 27 hrs.	4 cc. killed g.-p. in 5 hrs.[1, 3, 4, 6]	Aerobes and anaerobes	Aerobes and anaerobes

Symptoms in Injected Animals:

[1] Apathy, weakness, increased respiratory rate before death. At autopsy no peritonitis.

[2] Autopsy showed marked congestion of liver and spleen.

[3] Spastic seizure of hind limbs before death.

[4] Intense respiratory embarrassment before death. Autopsy showed emphysema.

[5] Velvety red congestion of duodenum and upper jejunum.

[6] Autopsy showed subendocardial hemorrhages.

The importance of bacteria in strangulation is further demonstrated by the fact that in the earlier stages of strangulation, when the peritoneal transudate has not yet become toxic, the outer layers of the wall of the strangulated bowel are sterile, as is, also, the peritoneal transudate itself. This can be easily

shown by the strangulation of bowel loops in rubber bags, if, at the time the fluid is collected, a biopsy specimen be obtained, with sterile precautions, from the seromuscular coat of the bowel, without opening the lumen (Table IX). If the fluid has become toxic, the seromuscular coat of the bowel gives a growth of aerobes and anaerobes in every case. In most, but not in all, of these later strangulations, the peritoneal transudate itself also gives a growth of organisms. The conclusion is inescapable that death in medium loop strangulation is due to infection of the devitalized bowel by bacteria from its lumen, and to the absorption by the peritoneum of the toxic products of their growth. It seems likely that the toxic euglobulin fraction of the peritoneal transudate contains the actual toxins of the bacteria, while the toxic diffusible fraction of the transudate contains the by-products of tissue destruction.

Knight[21] has shown that depressor substances are present in human cases of strangulation, not only in the peritoneal fluid, but in the blood within the veins of the strangulated segment of intestine. Knight and Slome[20] have further demonstrated that, in cases of strangulation, while the affected bowel loop still remains viable, a toxic effect is demonstrable in fluid obtained from the thoracic duct. In clinical cases of strangulation in man, it seems likely that death is due to a complex combination of pathologic factors, which include: (1) Diminution of effective circulating blood volume, in some cases at least, by loss of blood into the lumen of the strangulated bowel, into the bowel wall, and into the peritoneal cavity; (2) absorption of toxic transudate by the peritoneal cavity; (3) absorption of toxic material from the tissue spaces of the affected segment of bowel by lymphatic paths until these become closed as a result of circulatory stasis. It is common knowledge that a strangulated external hernia is a much less serious condition than strangulation of a bowel loop within the peritoneal cavity. This is almost sufficient clinical proof of the importance of peritoneal absorption of the toxic transudate. The sac of a hernia is capable of only slight absorption of the transudate from the strangulated loop which it contains.

Mention has been made in an earlier part of this paper of the depressor effect which sometimes follows relief of a simple occlusion of the bowel. An even more marked depressor effect occurs, in many cases, after relief of a still viable strangulation. Knight found, in animal experiments, that release of viable strangulations produced circulatory collapse and death in not less than 15 per cent of the animals used.[21] Here again, it would appear that during early strangulation, and the venous congestion which it produces, toxic materials from the lumen succeed in diffusing into the tissue fluids of the wall of the strangulated bowel, but fail to enter the general circulation, because of venous obstruction. When, however, the strangulation is relieved, the veins of the affected segment of bowel empty, circulation returns, and the toxin-laden fluid within the wall of the strangulated bowel can now reach the general circulation, to exercise a toxic, and sometimes lethal, effect. In fatal cases of strangulation in man, operation has nearly always been performed. At operation, the strangulated loops of bowel are closely inspected for signs of non-

viability. If the bowel appears to be viable, even though still congested, it is returned to the abdomen, and gradually, thereafter, recovers its normal circulation. It has long been known that whenever there is any doubt about the viability of a strangulated loop, it can be returned to the abdomen, as a rule, without any risk of gangrene and peritonitis. I would submit that the main risk in returning a strangulated loop to the abdomen is not the risk of perforation of that loop, but the danger that, in recovering its viability, there may be a return of toxic material from the wall of the strangulated bowel. This is a strong argument in favor of the more frequent resection, or, at least, exteriorization, of strangulated intestinal loops. "All recent experimental work has gone to show that when the least doubt exists as to the viability of the bowel, resection should be practiced, as continued toxemia from autolysis of cells and potential obstruction from imperfect peristalsis may lead to death some days after operation" (Wilkie[36]).

CONCLUSIONS

In high small intestine occlusion, the cause of death is dehydration, hypochloremia, alkalemia, and azotemia. These can be effectively controlled by nasal suction drainage and forced intravenous saline by drip. Operation may be delayed, and conservative measures continued for many days before operative relief of the obstruction, provided the cause of obstruction is known, and provided the presence of a strangulating element can be definitely excluded.

In untreated cases of low small intestine occlusion, whether in the experimental animal or in man, death does not occur, as a rule, until three or even four weeks after the onset of obstruction. In these cases, suspended absorption of water, salts, food materials, and other constituents of the intestinal content is sufficient to explain death. Gross congestion of the bowel is sometimes considerable before death in these cases, and leads in some, but not in all, animals to depletion of the blood volume. Perforation of the distended bowel and peritonitis is a relatively frequent cause of death in the animal or man whose occlusion remains unrelieved by operation.

To-day, the deaths from low small intestine occlusion are nearly all postoperative deaths. The toxic effect of sudden relief of a long-continued distention of the bowel has been demonstrated by experiment.

In occlusion of the colon, perforation and peritonitis are responsible for death in most cases. In long-continued colonic occlusion, the same factors probably operate as operate in low small intestine obstruction.

In closed loop obstruction, the cause of death depends upon the infectivity of the contents of the loop. In the case of the heavily infected closed loop, death is due to perforation and peritonitis. In the mildly infected closed loop, the same morbid influences are present as in low small intestine occlusion. Splanchnic congestion is usually more serious in closed loop than in simple occlusion.

In strangulation of short loops of bowel, death is due to perforation and peritonitis.

In long loop strangulation, death is due to diminution of the effective circulating blood volume, as a result of blood loss into the lumen and wall of the strangulated intestine, and into the peritoneal cavity.

In strangulation of loops of medium length, the cause of death appears to be the absorption of toxins. In the early stages of strangulation, this is by way of lymphatic routes, later by way of the peritoneal cavity.

The depressor effect of the sudden relief of any form of intestinal distention is seen in an exaggerated form upon the sudden relief of a long-continued strangulation.

A method is described of the establishment of chylothorax in the experimental animal, to furnish reservoirs of chyle for the purpose of experimental chyle transfusion.

The later experiments recorded in this paper have been performed in the Department of Surgery of the University of Edinburgh, under the direction of the late Sir David Wilkie, and of the Deputy Director, Mr. W. C. Wilson, now Regius Professor of Surgery in the University of Aberdeen. Many of the earlier experiments were performed in the Department of Surgery of Washington University, St. Louis, under the direction of Dr. Evarts A. Graham, and with the guidance of Dr. Robert Elman. The American experiments were performed during the tenure of a Rockefeller Traveling Scholarship, and the later part of the work in Scotland has been subsidized by a grant from the British Medical Research Council.

REFERENCES

[1] Aird, Ian: Loss of Blood from Circulation in Various Types of Intestinal Obstruction. Proc. Soc. Exper. Biol. and Med., **33**, 199, 1935.

[2] *Idem:* The Depressor Effect of Sudden Release of Intestinal Distention. *Ibid.*, **32**, 1593, 1935.

[3] *Idem:* The Morbid Physiology of Intestinal Obstruction. Thesis. Master of Surgery. University of Edinburgh, 1935.

[4] *Idem:* Intestinal Strangulation. Proc. Roy. Soc. Med., **29**, June (Sect. Surg., 51), 1936.

[5] *Idem:* Intestinal Obstruction: The Results of Recent Experiment Applied to Clinical Practice. Edinburgh Med. Jour., **43**, 375, 1936.

[6] *Idem:* The Rôle Played by the Diminution of the Effective Circulatory Blood Volume in Intestinal Obstruction. Edinburgh Med. Jour., **44**, 28, 1937.

[7] *Idem:* The Behaviour of the Blood Volume in Intestinal Obstruction and Strangulation. Brit. Jour. Surg., **26**, 418, 1938.

[8] *Idem:* De l'intoxication de l'occlusion aiguë. 2me congrès international de gastro-enterologie. Rapports et discussions. Paris, 1937.

[9] Aird, I., and Henderson, W. K.: The Histamine Content of the Peritoneal Transudate from Strangulated Intestinal Loops. Brit. Jour. Surg., **24**, 773, 1937.

[10] Bartlett, R. M., Bingham, D. L. C., and Pedersen, S.: Salt Balance in Surgical Patients. Surgery, **4**, 441, 1938.

[11] Best, R. R., Newton, L. A., and Meidinger, R.: Absorption in Intestinal Obstruction. Arch. Surg., **27**, 1081, 1933.

[12] Bottin, J.: Les occlusions aiguës et chroniques de l'intestin grêle. 2me congrès international de gastro-enterologie. Paris, 1937.

[13] Burget, G. E., Matzloff, K., Suckow, G., and Thornton, R. C. B.: The Closed Intestinal Loop. Arch. Surg., **21**, 829, 1930.

[14] Coller, F. A., Bartlett, R. M., Bingham, D. L. C., Maddock, W. G., and Pedersen, S.: Replacement of Sodium Chloride in Surgical Patients. ANNALS OF SURGERY, **108**, 769, 1938.

[15] Dick, B. M.: Personal Communication.

[16] Elman, R., and Aird, I.: Observations on Intra-intestinal Pressure with Special Reference to Absorption of Saline. Proc. Soc. Exper. Biol. and Med., **32**, 1620, 1935.

[17] Foster, W. C., and Hausler, R. W.: Acute Strangulation. Arch. Int. Med., **34**, 697, 1924.

[18] Herrin, R. C., and Meek, W. J.: Distention as Factor in Intestinal Obstruction. Arch. Int. Med., **51**, 152, 1933.

[19] Holt, R. L.: The Pathology of Acute Strangulation of the Intestine. Brit. Jour. Surg., **21**, 582, 1934.

[20] Knight, G. C., and Slome, D.: Intestinal Strangulation. Brit. Jour. Surg., **23**, 820, 1936.

[21] Knight, G. C.: Intestinal Strangulation. *Ibid.*, **25**, 209, 1937.

[22] Matthaes: Researches in Absorption from the Stomach and Intestine. Arch f. klin. Chir., **175**, 458, 1933.

[23] Maycock, W. d'A.: The Depressor Properties of the Peritoneal Transudate in Intestinal Strangulation. Brit. Jour. Surg., **25**, 677, 1938.

[24] Morton, J. J.: The Treatment of Ileus as Indicated by Clinical Experience and Experimental Studies. ANNALS OF SURGERY, **95**, 856, 1932.

[25] Mouchet, A.: Le Chylothorax Traumatique. Paris, A[illegible]te, 8vo, 297, 1933.

[26] Scott, H. G.: Experimental Evidence on the Loss of Bl[illegible] in Intestinal Strangulation. Arch. Surg., **36**, 816, 1938.

[27] Scott, H. G., and Wangensteen, O. H.: Experiments in Strangulation-Obstruction in Dogs. Proc. Soc. Exper. Biol. and Med., **29**, 424, 428, 559, 748, 1932.

[28] Scudder, J., Zwemer, R. L., and Truszkowski, R.: Blood Potassium in Acute Obstruction. Surgery, **1**, 74, 1937.

[29] Scudder, J., Zwemer, R. L., and Whipple, A. O.: Acute Intestinal Obstruction: Evaluation of Results in 2,150 Cases; with Detailed Studies of 25 Cases Showing Potassium as a Toxic Factor. ANNALS OF SURGERY, **107**, 161, 1938.

[30] Storck, A. H., and Ochsner, A.: Mechanical Decompression of the Intestine in Treatment of Ileus. Arch Surg., **33**, 664, 1936.

[31] Taylor, N. B., Welch, C. B., and Harrison, G. K.: Experimental Intestinal Obstruction. Canad. Med. Assoc. Jour., **29**, 227, 1933.

[32] Treves, Sir Frederick: Intestinal Obstruction. London, Cassell & Co., Ltd., 1899.

[33] Wahren, H.: Experimental Strangulation of Intestine. Acta Chir. Scandinav., **78**, 121, 1936.

[34] Wangensteen, O. H.: Bowel Obstructions. London, Baillère, Tindall & Cox, 1937.

[35] Wheeler, Sir W. I. de C.: Significance of Recoil Following Visceral Decompression. Canad. Med. Assoc., Jour., **24**, January, 1931.

[36] Wilkie, Sir D. P. D.: Acute and Chronic Obstruction of the Small Intestine. 2me congrès international de gastro-enterologie. Rapports et discussions. Paris, 1937.

[37] Wohl, M. G., Burns, J. C., and Clark, J. H.: Adrenal Glands in Dogs with High Intestinal Obstruction. Proc. Soc. Exper. Biol. and Med., **33**, 543, 1936.

THE MUSCULAR ACTIVITY OF THE SMALL INTESTINE, IN THE DOG, DURING ACUTE OBSTRUCTION

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Stone and Firor, in 1924, reported that in cases of temporary obstruction of the terminal ileum in the human (duration five hours or less), pressure within the ileum rose as high as 150 cm. of water, and suggested that the extremely high pressure in obstructed intestine contributes to the toxemia, probably by facilitating absorption of hypothetical toxins. Herrin and Meek[2] have further emphasized the importance of pressure in the pathologic mechanism by producing symptoms of obstruction in dogs by the inflation of balloons within the intestine to pressures of approximately 100 Mm.Hg. (135 cm. aq.). It has been shown, however, that if by-passes are provided so that balloons inflated to these pressures do not actually obstruct the intestine, the animals go on to death without a significant lowering of blood chlorides.[3] Since hypochloremia is one of the cardinal signs in obstruction in dogs, and since life may be greatly prolonged by administering chlorides,[2] it may be doubted that the pathologic mechanism in dogs dying from overdistention of intestinal balloons is identical with the mechanism in dogs dying from other forms of obstruction.

The clinical significance of much of the experimental work which has been done in the dog with overinflated balloons remains obscure unless it can be established that pressures of similar magnitude develop within the intestine obstructed by ligation or simple occlusion of the lumen. There is no question that closed loops and the entire bowel above a simple occlusion become distended with gas and secretions in the dog as well as in the human. That strangulation may result from overdistention was first suggested by Van Zwalenburg,[4] in 1907. Data obtained in this laboratory show, however, that distending pressures must usually rise above 30 Mm.Hg. in dogs under barbital anesthesia before there is reduction in blood flow.[5] In the light of these data, it would appear that distention may produce damage by ischemia only if it rises, during the course of obstruction, above a certain critical level. Since the circulation through active and inactive intestine may not be equally affected by a given distending pressure, the question of adynamic ileus as a constant terminal phenomenon in obstruction has more than academic interest.

The pressures which have been reported to occur within obstructed small intestine in the dog are considerably below those used in experiments with overinflated balloons. Owings, McIntosh, Stone, and Weinberg[6] found

average "tone," or resting pressure in simple obstruction to be 6–8 cm. aq., with pressure rising to 30–60 cm. during maximum contractions. In closed loops Burget, Martzloff, Suckow, and Thornton[7] measured an average pressure of 39.5 cm. aq. Sperling, Paine, and Wangensteen[8] found pressures from 4 to 19 cm. aq. in simple obstruction of the lower ileum.

Hypermotility during the early stages, and adynamic ileus, as a terminal phenomenon, have come to be clinically accepted as characteristics of the obstructed bowel. In experimental obstruction, hypermotility has been observed more frequently than ileus,[6, 8, 9] and in studies in which attention has been directed to this detail, terminal ileus appears to be associated with peritonitis.[6] There is, thus, no evidence for terminal ileus in uncomplicated obstruction in the dog.

In view of the importance of these details for an understanding of the immediate pathologic mechanism in obstruction, and the incomplete information available, we thought it worth while to make a more extended study of muscular activity in obstructed intestine in the dog.

Methods.—All operations were performed on healthy adult dogs, under ether anesthesia, with strict asepsis. At the time of operation a large condom balloon was inserted through a stab-wound in the antimesenteric border of the intestine so as to lie in an obstructed segment. This was accomplished by passing the balloon in an oral direction and tying the obstructing ligature (soft, round cotton yarn) tightly down upon its lead tube, the latter being made rigid by insertion of a short length of glass tubing. The stab-wound, about 1 cm. below the obstructing ligature, was then closed about the lead tube by Witzel's method. This procedure avoided the placement of a suture line, through which leakage might occur, in obstructed intestine.

In some animals a balloon was also placed, at the same time, in distal unobstructed intestine through a stab-wound about 5 cm. below the first, the balloon being passed in an aboral direction. The lead tubes from the balloons were brought out and anchored in the belly wound which was closed in the usual manner.

Most of our observations were made upon dogs with closed loops of the first portion of the jejunum, about 15 cm. below the ligament of Treitz, prepared by simple ligation at this level, with a second ligation upon the lead-tube of the recording balloon 10–12 cm. below, the balloon lying between the two ligatures. It was intended to compare these closed loops with simple obstructions, in which it is generally agreed that pressure is lower. But our data on the closed loops showed such low pressures that we felt a complete comparison unnecessary.

That necrosis and perforation at the ligature will occur with this type of obstruction, if the animal survives long enough, is generally agreed. Most of our animals died 48–72 hours after operation, the short survival time being, doubtless, in part due to the fact that we gave no fluids or other supportive treatment. Autopsies were performed as soon as possible after death in all. Ten animals out of a series of 27 were found to have perforated

loops. In the others there was no demonstrable perforation or peritonitis. With these exceptions, therefore, our data may be taken as showing the course of events leading to death from uncomplicated obstruction.

All observations were made without anesthesia, with the animal, after a brief period of training, lying quietly on a pad. The first observation was made 4–24 hours after the operation, and subsequent observations were made at intervals of 8–18 hours. Preliminary to making an observation, the balloons were inflated and deflated a few times to make sure that they were not twisted or kinked, completely emptied of air under negative pressure, then filled from a syringe with 15 cc. of air measured at atmospheric pressure. The lead tubes were then connected with water manometers, and a kymograph record, lasting 75–120 minutes, was made. Since the balloons had a tested capacity of 50 cc. at atmospheric pressure outside the intestine, their pressure readings at a volume of 15 cc. are approximately equal to intra-intestinal pressure. Complete expulsion of the 15 cc. of air from the balloon into the manometer gave a pressure reading in the manometer of approximately 40 cm. aq., which is higher than our highest measurements.

Any attempt to express a change in intestinal motility in quantitative terms, is open to the criticism that the features chosen for quantitation may not be representative. All workers in the field have observed simultaneous changes of different degree or direction in such various indices of motility as tone, contraction height, size and frequency of tonus waves, and rhythmicity of pendular movements. In the absence of any general agreement upon some one satisfactory index to intestinal motility, we have made separate measurements of these individual functions as defined below.

Results.—Minimum Pressure: This was measured as the lowest pressure recorded at any time during each period of observation. Since it is read during the interval between contractions, it represents what would usually be called minimal "tone" for each tracing.

In ten animals who were prepared with balloons in the distal, unobstructed jejunum for comparison, we were able to make a total of 25 comparative readings of minimum pressure in obstructed and unobstructed intestine. In 19 of these paired observations, minimum pressure was significantly higher in the obstructed loop. In every animal except one, minimum pressure was elevated in the obstructed loop over its unobstructed control on the first reading (Table I).

As will be seen from examination of Table I, our irregular intervals of observation fail to show the time required for pressure to reach its peak in the obstructed loops. Nineteen animals appear in the table upon whom more than one observation was made. In eight of these, pressure was highest at the first reading. It is possible that the peak of pressure has escaped observation in some, but this is unlikely since, with a few exceptions, there is close agreement of the readings at the peak of the pressure elevation.

The average of the minimum pressures at the time of their greatest elevation (series of 27 dogs) was 16 cm. aq. The highest observed minimum

pressure was 27 cm. aq. As was expected, the average of the closed loops was somewhat higher than the average of the small series of simple obstructions (four animals—average minimum pressure at peak of elevation 14.5 cm. aq.). The average of the minimum pressures at the time of their greatest elevation in the ten dogs with balloons in distal, unobstructed jejunum was 10.0 cm. aq.

TABLE I

Dog No.	Segment	Minimum Pressure Cm. Water					Maximum Pressure Cm. Water					Contractility Mm. Water				
	Obs. No.	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
1	Distal	9	8	9	5		10	10	16	7		9	10	8	23	
	Obstr.—(p)*	17	14	16	3		32	26	28	25		65	55	11	52	
2	Distal	10					12					4				
	Obstr.—(p)	14					19					17				
3	Distal	8	9				9	10				8	14			
	Obstr.	9	12				17	30				20	90			
4	Distal	8	8				16	24				26	46			
	Obstr.—(p)	14	9				30	12				50	11			
5	Distal	9	10	11	11		13	12	16	14		7	5	9	11	
	Obstr.—(p)	11	27	3	5		15	28	11	7		10	5	5	4	
6	Distal	6	5	—	—		8	6	—	—		8	4	—	—	
	Obstr.	10	18	14	15		13	23	17	28		9	20	8	55	
7	Distal	6	19	—			13	23	—			12	15	—		
	Obstr.	18	14	6			26	20	14			18	20	42		
8	Distal	11					12					2				
	Obstr.	24					26					3				
9	Distal	8	9	12			9	10	17			5	5	11		
	Obstr.—(p)	8	—	11			14	—	16			30	—	7		
10	Distal	13	8	12	5	12	17	11	14	6	14	13	5	3	3	3
	Obstr.	23	11	12	12	15	26	15	17	22	26	17	15	17	40	50
11	Obstr.	12					14					8				
12	"	20	7				22	8				11	7			
13	"	9	10	9	10		11	12	22	33		10	17	46	80	
14	" —(p)	14	12	10			19	23	17			15	31	35		
15	" —(p)	12	5				15	12				3	27			
16	"	3	12	8	13		6	31	30	31		11	65	75	56	
17	"	6					9					17				
18	" —(p)	18	10				24	11				31	2			
19		19					20					10				
20	"	6	8				28	27				65	48			
21	"	5	9				9	24				16	28			
22	"	7					21					35				
23	"	4	13	15	8	7	6	28	25	15	15	4	55	40	34	38
24	"	18	17	16			30	28	21			5	3	20		
25	" —(p)	16					19					15				
26	" —(p)	21					27					28				
27	"	15	25				23	28				15	8			

* p denotes perforation demonstrated at autopsy.

Of the 19 animals, upon whom serial observations were made, nine showed a definite diminution in minimum pressure toward the end of their survival period. In six of these, perforation was found at autopsy. Neither perforation nor peritonitis could be demonstrated at autopsy in any of our other animals.

Maximum Pressure.—This was taken as the highest pressure recorded at any time during each period of observation. Respiratory records were taken routinely by means of a pneumograph to ensure that our readings of maximum pressure were not influenced by such modified respiratory acts as vomiting and defecation. The data which we obtained may be taken to

represent the maximum pressure developed within the intestine by the muscular activity of the intestine.

In the ten animals with balloons in both obstructed (closed loops) and unobstructed (distal) jejunum, we made a total of 25 paired observations on maximum pressure. In 20 of these, pressure rose higher in the obstructed than in the unobstructed intestine. In all animals, maximum pressure was elevated in the closed loop over its distal control at the first observation (Table I). In the entire series of 27 dogs, the average of the maximum pressures taken at the time of their greatest elevation was 26.8 cm. aq., the highest single reading being 33.0 cm. Of the 19 dogs available for serial observations, only nine showed a terminal fall in maximum pressure. As shown in Table I, these are, with two exceptions (Dogs 7 and 24), the animals whose minimum pressure declined terminally, and in whom perforation was demonstrated at autopsy. That perforation does not necessarily suppress contractility is shown by the observations on Dog 15, in whom perforation was demonstrated at autopsy two and one-half hours after the last observation was made. Only three of the animals with terminal decline in contractility were prepared for observations on distal intestine (Dogs 4, 5 and 9). In none of these was contractility suppressed terminally in the distal control intestine (Table I).

Contractility.—It is obvious that intra-intestinal pressure may be either a function of the muscular activity of the intestine, or the result of passive stretching of the walls of the intestine by its contents. Pressure is, therefore, an uncertain index to the muscular activity of the intestine. Nor are the pressure changes (obtained by subtracting minimum from maximum pressure) much more reliable, since under some conditions intense muscular activity may result in the maintenance of steady high pressure for long periods of time, and since, on the other hand, secretion, transudation, or hemorrhage may cause rather abrupt changes in the volume of intestinal contents. Clearly recognizable muscular functions of the jejunum result in the appearance on the pressure records of (a) simple pressure waves at a frequency of 6–20 per minute, due to the pendular movements; and (b) tonus waves with a duration of 1–3 minutes, upon which the pressure record of the pendular movements is superimposed. We have measured the amplitude in each tracing of these two types of pressure change, and have taken as a measure of contractility the maximum pressure change of either type, which occurred during each period of observation. These pressure changes are recorded in Table I under "contractility" without distinction between the two types.

Twenty-six paired observations on obstructed and unobstructed intestine were made in ten dogs. Maximum contractility as measured in this manner was greater in the obstructed than in the unobstructed intestine in 22 observations. Among the 19 dogs upon whom serial observations were made, there was a definite terminal reduction in contractility in only six animals (Dogs 4, 5, 9, 12, 18 and 27). Four of these (Dogs 4, 5, 9 and 18) showed

a terminal fall in minimum pressure, and were found at autopsy to have perforated loops.

Rhythmicity.—The rhythm recorded by the pendular movements on large balloons, such as we used, is of doubtful significance. A rapid beat on the record may mean a rapid beat of a single fascicle of smooth muscle, or it may mean the summation on the record of a number of slowly beating fascicles contracting and relaxing asynchronously. The use of smaller balloons, or of enterographs recording smaller areas of smooth muscle, reduces, but does not remove this error. We obtained data on rhythmicity as recorded by the pendular movements on our records, fully aware that our methods were inadequate, in the hope that some striking change might be observed which would justify an attempt at interpretation. Since this hope was not realized, the possibility remains that adequate studies on rhythm would show striking changes in obstruction.

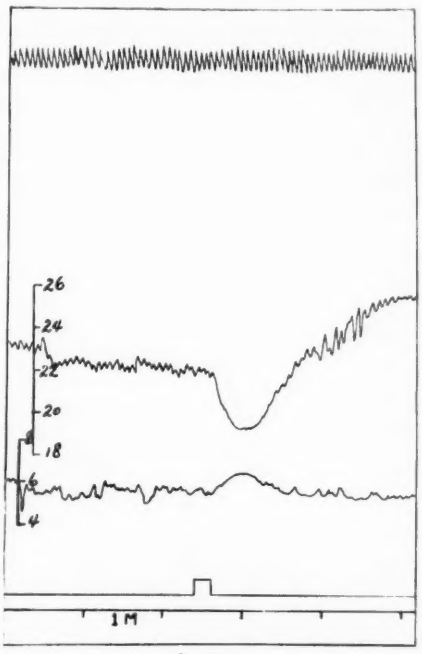
In our studies, the rhythm of the pendular movements appeared to be at a maximum during the intervals between tonus waves. The average for all dogs, in the unobstructed distal jejunum, at this time was 16.2 beats per minute, in the obstructed, closed loops, 16.3 beats per minute. Usually there was appreciable slowing of rhythm on the records toward the peaks of tonus waves. The average for all dogs at this time in the unobstructed distal jejunum was 14.2 beats per minute, in the obstructed loops 12.7 beats per minute. Examination of individual pairs of observations fails to show a consistent difference in the rhythm of the obstructed and of the unobstructed intestine. Out of 24 such paired observations on minimum rhythm (at the peaks of the tonus waves) the rhythm was greater in the obstructed loop, eight times, greater in the unobstructed loop, ten times, and the same in both, six times. Out of 22 observations on maximum rhythm (at the troughs of the tonus waves) rhythm was greater in the obstructed loop 16 times, in the unobstructed loop, five times, and the same in both, once.

Effect of Epinephrine on the Obstructed Intestine.—Data on the response to intravenous epinephrine were obtained in an attempt to determine: (1) Whether the increase in minimum pressure in the obstructed intestine is due entirely to distention of the intestine by an increase in its contents; and (2) whether the increase in contractility is due to diminished sensitivity to inhibitory agents.

To answer the first question, we injected moderately large doses of epinephrine (usually 0.02–0.04 mg. in a volume of 1 cc.) at a time when minimum pressure was markedly elevated. In a series of 24 animals, studied in this way, epinephrine caused a significant drop in minimum pressure in the obstructed loop in every case (Graph 1).

To answer the second question, we determined the threshold dosage of epinephrine, under standard conditions, in a series of six dogs at intervals during the survival period. All of these animals were prepared with balloons in distal, unobstructed intestine for comparison. All doses were made up in a volume of 1 cc. and injected as rapidly as possible in the posterior crural

vein. The doses were adjusted at each observation until a just-detectable reduction in either tone or contractions was obtained, and each dose near the threshold was repeated two or more times to check the determination. No consistent difference in the threshold for the obstructed and the unobstructed intestine at any time during the survival could be established in this series of animals. In all six animals, however, there appeared to be a progressive lowering of the threshold in both the obstructed and the unobstructed intestine (Table II).



Graph 1.

GRAPH 1.—The Response of the Obstructed Intestine to Epinephrine: Records from above down—Respiration by pneumograph; balloon record of doubly-ligated jejunal loop; balloon record of distal unobstructed jejunum. Intra-intestinal pressure in centimeters of water. Duration of obstruction 23 hours. At the signal 0.005 mg., epinephrine in 1 cc. saline was injected into the posterior crural vein. The rise in pressure in the unobstructed loop is not unusual in atonic intestine.

Discussion.—It was not our purpose in this study, to maintain animals surviving obstruction in optimum clinical condition. It is possible that our results would have been somewhat different had we done so. Our data show, however, that dogs may go on to death without the development, even in closed loops, of excessively high intra-intestinal pressures. Such pressures as we have observed do not, in anesthetized dogs, reduce the total blood flow through the intestine.[5] They are far below the pressures employed in obstructing balloons for the production of symptoms. Whether these moderate pressures, maintained in non-obstructing balloons, will produce symptoms in the dog has not yet been determined.

That our data on the pressures prevailing in obstructed intestine are fairly accurate is shown by their approximate agreement with the statistics of previous workers.[7, 8, 9] It might be expected that our readings would be high, since our methods required the inflation of a balloon within the loop, thus increasing the volume of intestinal contents. That they are somewhat lower than those previously reported[7] for closed loops may be due to the absence of supportive postoperative treatment in our dogs. Details of postoperative treatment are not given in most of the previous reports.

Our data suggest, in confirmation of Owings, McIntosh, Stone, and Weinberg,[6] that terminal ileus is a concomitant of peritonitis rather than of obstruction. In only three animals, in a series of 20, did we find a terminal reduction in muscular activity (using any single criterion of motility) unaccompanied by peritonitis secondary to perforation. In half our animals no terminal reduction in motility was demonstrable.

It is not possible to say, from our studies, whether rhythm in the obstructed intestine is modified. The limitations imposed by our methods were pointed out above. These limitations are such as to permit us to say only

TABLE II

THRESHOLD INTRAVENOUS DOSAGE OF EPINEPHRINE IN OBSTRUCTED AND IN DISTAL SEGMENTS

Dog No.	Duration of Obstruction Hours	Dose (Mg.) in 1 Cc.	
		Distal	Obstructed
1	9	0.0100	0.0100
	14	0.0081	0.0081
	23	0.0055	0.0055
2	5	0.0028	0.0028
	23	0.0025	0.0010
	33	—	0.0010
3	10	0.0280	—
	28	0.0028	0.0028
	53	—	0.0028
4	8	0.0400	0.0400
	30	0.0280	0.0280
5	12	Motor	0.0280
	28	0.0020	0.0050
	48	0.0033	0.0033
6	23	0.0200	0.0400
	33	0.0050	0.0200
	48	0.0020	0.0020

that we obtained no evidence in favor of Alvarez's[10] hypothesis that a reversal of the rhythmic gradient is responsible for stasis and vomiting in obstruction, since we demonstrated no such change in the rhythm of the obstructed intestine as his theory requires.

Additional evidence that the adynamia of the obstructed intestine in the terminal stages is far from complete, is adduced from the fact that the intestine may be inhibited by epinephrine. The significance of an apparent increase in sensitivity to epinephrine in both the obstructed and the unobstructed intestine in terminal stages requires elucidation. It seems clear, however, that hypermotility in the obstructed intestine is not due to a loss of irritability to inhibitory agents of this type.

SUMMARY

Balloon studies of motility in obstructed jejunal loops were undertaken in unanesthetized dogs at intervals, so long as the animals survived. Comparisons were made in some animals with motility in unobstructed distal segments. The following data were obtained:

(1) At the time of the greatest increase in intra-intestinal pressure, maximum pressure in the obstructed loops averaged 26.8 cm. aq., with the highest single reading 33.0 cm. aq. Minimum pressure at the time of its greatest elevation averaged 16 cm. aq. The range of pressure in closed loops is con-

siderably above the range in distal, unobstructed intestine (average maximum 15.6 cm. aq., average minimum 10.0 cm. aq.).

(2) Contractility was usually considerably greater in the obstructed than in the unobstructed intestine.

(3) Neither pressure nor contractility was found to diminish toward the end of the survival period unless perforation occurred. Even in the presence of perforation, active contractions sometimes occurred.

(4) No loss in irritability to intravenous epinephrine could be demonstrated in obstructed intestine. Even in terminal stages, the response to sufficiently large doses was a drop in pressure within the intestine, showing persistence of some muscle tone.

(5) The bearing of these data on the theory that pressure within obstructed intestine damages the intestine is discussed.

REFERENCES

[1] Stone, H. B., and Firor, W. M.: Absorption in Intestinal Obstruction, Intra-intestinal Pressure as a Factor. Tr. South. Surg. and Gynec. Assn., **37**, 173, 1924.

[2] Herrin, R. C., and Meek, W. J.: Distension as a Factor in Acute Intestinal Obstruction. Arch. Int. Med., **51**, 152, 1933.

[3] Taylor, N. B., Weld, C. B., and Harrison, K.: Experimental Intestinal Obstruction. Canad. Med. Assn. Jour., **29**, 227, 1933.

[4] van Zwalenburg, C. V.: Strangulation Resulting from Distension of Hollow Viscera. ANNALS OF SURGERY, **46**, 780, 1907.

[5] Lawson, Hampden, and Chumley, J.: The Effect of Intra-intestinal Pressure on Blood Flow Through the Intestine. Proc. Am. Physiol. Soc., **52**, 105, 1940.

[6] Owings, J. C., McIntosh, C. A., Stone, H. B., and Weinburg, J. A.: Intra-intestinal Pressure in Obstruction. Arch. Surg., **17**, 507, 1928.

[7] Burget, G. E., Martzloff, K., Suckow, G., and Thornton, R. C. B.: Relation of Intraloop Pressure to the Clinical Condition of the Animal. Arch. Surg., **21**, 829, 1930.

[8] Sperling, L., Paine, J. R., and Wangensteen, O. H.: Intra-enteric Pressure in Obstruction. Proc. Soc. Exper. Biol. and Med., **32**, 1504, 1935.

[9] Carlson, R. A., and Wangensteen, O. H.: Motor Activity of the Distal Bowel in Intestinal Obstruction. Proc. Soc. Exper. Biol. and Med., **27**, 676, 1930.

[10] Alvarez, W. C.: An Introduction to Gastro-enterology. New York, Paul Hoeber, Inc. 1940.

THE SIGNIFICANCE OF NEUROMATOUS LESIONS IN OBLITERATED APPENDICES

A CLINICOPATHOLOGIC STUDY

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THE SURGEON, confronted by the patient with complaints of abdominal pain (epigastric, right lower quadrant or diffuse) temporarily aggravated, encounters symptoms suggestive of appendicitis but is frequently unable to elicit objective evidence of such. Physical examination of these patients may disclose tenderness in the right lower quadrant, most frequently on deep pressure, but rarely muscle rigidity. Temperature levels and leukocyte counts are frequently within normal range. The patient may give a history of long standing abdominal distress, frequently with a recollection of its inception in an episode characterized by acute pain. Often, long standing, mild abdominal discomfort is punctuated by attacks of acute distress, occasionally with some history of slight fever. As frequently, a history of dietary indiscretion is obtained. If encountered in a subjectively quiescent stage or after the subsidence of what historically resembles an acute attack of appendicitis, the patient may, if indicated, be operated upon with a diagnosis of interval appendix, chronic or subacute appendicitis. The pathologic reports are variable, in only some instances consistent with the clinical picture. The clinical entity, chronic appendicitis, only rarely receives strict morphologic confirmation.

On those occasions when the preoperative diagnosis is acute or recurrent appendicitis, the histologic diagnosis is not infrequently at variance with the clinical diagnosis. The attitude of the surgeon may, in such instances, be one of chagrin or confusion. This attitude, however, may be somewhat mollified by his recollection of the operative picture which disclosed to him an explanation of the symptoms which he had interpreted as inflammatory, such as the presence of bands, twists or kinks which may produce mechanical symptoms.

To the confused surgeon and the surgeon-harassed pathologist, the entity "neurogenic appendicitis" should offer a promising solution of these numerous instances of so-called chronic appendicitis. Since its description in 1921, this subject has commanded the attention of a number of authors to whose opposing opinions probably may be attributed the fact that neurogenic appendicitis as an entity has been accepted with some diffidence. Some authors deny its existence and the neurogenous nature of lesions occurring in the involved appendices; others, agreeing to the nervous nature of certain lesions observed

in appendices, question the clinical significance of these or the likelihood of a diagnosis of neurogenic appendicitis being made with certainty preoperatively; the proponents of the entity are clamorous for its further clinical confirmation.

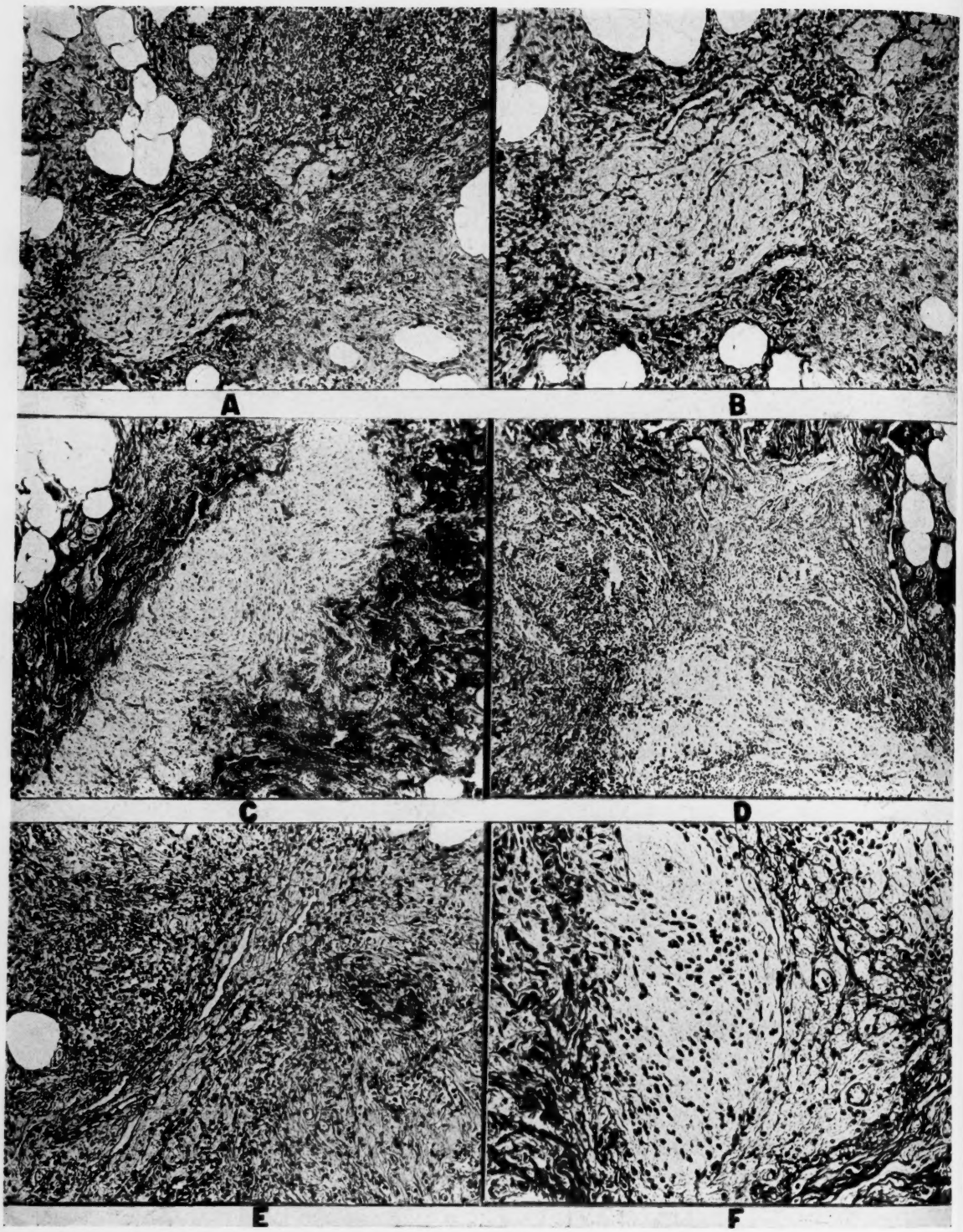
As examples of the varied evaluations of the subject, the following are listed: Masson[1] and Maresch,[2] in 1921, almost simultaneously, described lesions in the obliterated appendix. Both authors considered the lesions as sympathetic neuromata. Subsequently, Masson[3] altered his interpretation of these from sympathetic neuromata, which he had initially likened to amputation neuromata, to argentaffin neuromata. The latter he considered to be proliferations of mucosal nervous tissue stimulated by argentaffin cells with which they are associated.

Both the above authors regarded these lesions as having been provoked by previous inflammations. Masson,[3] in 1922, believed that a banal ulcerative process, sufficiently intense to be irritative but sufficiently slight to be nondestructive of the epithelium and contemporaneous with the normal neurogenic impulse, provokes hyperplasia of the preexisting neuro-argentaffin tissue which becomes enmeshed in the cicatricial tissue. His original disposition of these structures as amputation neuromata caused by division of the sympathetic filaments of the mucosa by an ulcerative process, he[4] considered unsatisfactory, in that the neuromata always contain argentaffin cells and amputation neuromata do not contain these. Masson[4] also discussed the possibility of the periglandular plexus from which these neuromata arise being, not of sympathetic origin, but dependent genetically on certain entodermic cells and that it represents a placode, a neurentoderm.

Urech,[5] in 1928, found among 400 appendices removed in the quiescent period after acute attacks of appendicitis, 16 obliterated, in which neural proliferation was prominent. Urech stated as a hypothesis that the lesions may be attributed to more or less discrete inflammation which escapes the attention of the patient. This author further stressed that the superabundance of nervous tissue which has been wrongly or reasonably compared to amputation neuromata explains the important place that pain plays in this clinical entity and the happy results after operations of patients without inflammatory lesions. This author further stated that if the diagnosis could be foreseen preoperatively, it would be affirmed only exceptionally. (He also noted that two-thirds of the cases occurred in women, and presented the variety of symptoms which are ordinarily classified as nervous.)

Hosoi,[6, 7] in 1933, presented pathologic findings and the clinical features of 344 consecutive cases, 56.7 per cent containing neuromata, 48 per cent of the 344 showing some degree of obliteration. These cases were presented as instances of neurogenic appendicitis and were supposedly operated upon because of symptoms which could be attributed to nervous irritation. In the histories of many of these patients, previous incidents simulating appendiceal crises were described.

Simard,[8] in 1935, stated that nervous alterations alone may give rise to



A.—Presence of proliferated nerve fibers in the center of an obliterated appendix. Note the accumulation of lymphocytes adjacent to the nerve fibers. (Hematoxylin-eosin preparation; ×60)

B.—Same as A. (Hematoxylin-eosin preparation; ×80)

C.—Large nerve bundles in an obliterated appendix. (Masson stain; ×56)

D.—Presence of nerve bundles adjacent to much lymphadenoid tissue in the center of an obliterated appendix. (Masson stain; ×60)

E.—Lymph follicles and nervous elements in close approximation. (Hematoxylin-eosin preparation; ×80)

F.—Nerve cells and fibers adjacent to old connective tissue fibers in the center of an obliterated appendix. (×160)

characteristic symptoms of acute appendicitis such as stabbing pain, muscle guarding, *etc.* He previously had made the suggestion that in the presence of clinical signs and symptoms pointing to acute appendicitis, when leukocyte count is at or near normal, and disease of the kidney, ovary or gallbladder may be excluded, the diagnosis of neuro-appendicopathy can often be made with assurance.

Fein, Hanan and Seidler,[9] in 1938, listed 202 neuromata among 600 appendices, 140 occurring in appendices with varying degrees of obliteration. Twelve and one-tenth per cent of neuromata were in appendices showing acute suppurative inflammation; 26.8 per cent were associated with subacute appendicitis.

Llombart,[10] in 1938, in investigating the anamneses of ten patients, stressed that, in general, one might state that definite attacks, often with fever and muscle guarding, precede nervous hypergenesis and that it might be supposed that obliteration was initiated at such a moment and the nerves contained within the obliterated zone hypertrophied. Though this author believed it almost logical to suppose the nervous lesions incitants of the clinical symptoms, he stated that it is impossible at present to know whether repeated attacks (simulating appendicitis) favor the development of neurogenic appendicitis or, on the contrary, the repetitious complaints are the consequence of the nervous lesions. He was impressed with the rapidity with which this nervous hypergenesis was established. This author succeeded in demonstrating nerve fibers by the use of specific silver stains.

Rossle,[11] in 1930, pointed out that not only central neuromata in recently obliterated appendices but also neuromatosis of the intact mucosa and submucosa are able to produce appendiceal complaints, the latter largely because of alterations of the neuromuscular apparatus which, in interfering with evacuation, provokes symptoms. However, he considered the neuromata to be proliferations of the Schwann's syncytium and as such but a single feature of pathologic alteration of the nervous apparatus.

Among the opponents of the neurogenous etiology of these structures may be mentioned the following:

Schweizer,[12] in 1922, describing "neuromartige" in obliterated appendices, and presenting pictures of lesions almost identical with or at least very similar to those of Masson,[1] took exception to Masson's interpretation of these lesions. He evaluated them as neurinomata and questioned their relation to symptoms in that many were noted in autopsy specimens from subjects of advanced age. This author further stressed the high incidence of argentaffin cells and was inclined to consider these structures derivatives of the sympathetic fibers surrounding the crypts and the muscularis mucosa.

Schack,[13] in 1932, believed the so-called neuromata to be, not primary proliferations of nerves, but a disease or alteration of the reticulum, and that the finding of nerve fibers within them is only incidental in that nerve fibers spreading as a net with and between the reticulum cells are only naturally included within a tumor of the reticulum. He considered these irregular

growths the indirect consequence of inflammatory irritation. This author was unable to prove the existence of an anatomic disease in the sense of neurogenic appendicitis and evaluated the neurogenous tissue as a residuum of inflammation.

Collins,[14] in 1936, in reviewing a large number of surgical and autopsy specimens, was unable to find indication of nervous proliferation as the provocative element in obliteration. He considered this largely induced by inflammation which progressed to granulation tissue. Though no illustrations were presented, it was the contention of this author that the axial lesions in obliterated appendices are composed of granulation tissue.

That structures other than adult fibrous connective tissue occur in the axis of the partially or completed obliterated appendix is unquestioned. The interpretation of these may or may not be of merely academic interest. If they are neuromatous in nature the surgeon, cognizant of the confusion involving the mechanism of abdominal pain, asks, "What do they mean, and are they, *per se,* responsible for this pain?"

The presence of nerve fibers in the mucosa of the intestinal tract has been demonstrated by numerous authors, and specifically in the appendix by Reiser,[15] who speaks of a nervous spongiosa. The quantity of these nerve fibers is considered to be so great that some authors think they compose the main mass of the mucosa (Masson[16]). However, the possession by these nerves of sensory functions is open to dispute. Thus Hill,[17] from a study of the intestines of animals, concluded that the mucosa and subserosa are endowed with sensory function. Masson[18] likewise attributed to the mucosal fibers sensory functions. He considered "a nervous system peculiar to the intestinal mucosa, of entodermic origin . . . the neurites of which . . . mingle with those of the sympathetic and form the plexus of the mucosa." This plexus, according to Masson, "contains two kinds of fibers, the one centripetal, belonging to the neurentoderm, the other centrifugal, starting from the sympathetic ganglia and arriving at the intestinal surface." He also stated that, because of the organogenic analogies of the hypothetic system with the argentaffin cells, and the placodic neuro-epithelium of the olfactory mucosa, he had thought that its function might be sensory rather than motor. Histologic studies by many investigators have failed to produce definite evidence of sensitivity, most authors considering this property of the mucosa a possibility rather than a fact. Reiser,[15] Schack,[13] Oshima[19] and Ranson,[20] on the other hand, stated that in spite of the negative character of the histologic evidence, the existence of sensory fibers in the gastro-intestinal mucosa has been assumed by most physiologists. The clinicophysiologic evidence would implicate the muscularis rather than the mucosa of the hollow viscera in the sensation of fulness or pain (Hertz,[21] Ryle,[22] Morley,[23] Kuntz,[24] *etc.*).

It may be of interest in this connection to consider, in short, the present concept of the origin of "appendiceal" pain. Actually most clinicians consider the pain in diseases of the alimentary canal to be most frequently true visceral pain (Capps,[25] Hertz[21]). But visceral pain is usually attributed to

muscle tension. Most authors consider the only adequate stimulus for this type of pain to be abnormal increase in the tension of the muscular elements produced by distention of the viscus, some suggesting undue contraction which in bringing pressure to bear upon the nerves in the wall of the hollow viscera, may produce pain. The pain involved in undue contraction, however, is generally considered to be the result of distention of a neighboring segment of bowel. Hertz[21] considered that true visceral pain occurs only in those lesions in which there is abnormal motor activity. Interesting in this connection is Masson's[1] original suggestion in regard to neuromatous lesions—that they represented sympathetic neuromata enclosed in a double muscle layer, every contraction of these muscles forcibly compressing them. He believed that if they contained neurites in communication with the appendiceal plexus, they may be a point of departure of more or less important reflex difficulties.

To implicate the axial lesions in the tenderness elicited in these patients, one might best consider the tenderness as referred, a viscerosensory reflex, and accept the autonomic nerve fibers as the afferent paths for the transmission of stimuli arising in the appendiceal lesion. While this evaluation would appear to be the logical one, we are reminded that the tenderness is evoked generally, by very deep palpation. This may produce traction on the mesentery, and peritoneal irritation or by the compression of a tense viscus, splanchnic pain. With reference to this we may recall a statement of Hertz[21] that "referred pain, the result of the arrival in the spinal cord of impulses from an internal organ, is comparatively rarely present alone, as the impulses from the internal organ generally themselves give rise to visceral pain. But pain originating in the peritoneum in connection with disease of the alimentary canal is not uncommon in the absence of visceral pain." To further obscure the situation one may recall another observation of this author[21] that "visceral sensibility is exaggerated by training in hypochondriasis and visceral and referred sensations are exaggerated by the irritable condition of the central nervous system in neurasthenia and anemia."

Realizing the complexity of concepts of the origin of visceral pain, it seems evident why the presence of nervous elements in certain appendices has been linked with pain felt by the respective patients. Though efforts have been made to establish a symptom complex fairly pathognomonic of neurogenic appendicitis (Hosoi,[7] Llombart,[10] Montandon,[26] Simard[8]), only a few investigators have satisfied themselves that such a symptom complex actually exists. Urech,[5] Montandon[26] and Schack[13] definitely doubted the possibility of a preoperative diagnosis of neurogenic appendicitis being made. While the histories of many patients having neuromatous lesions of the appendix may be suggestive, the objective findings are not too distinctive.

In an attempt to evaluate the significance and faculties of these controversial lesions in the appendix, we accept the theory of Masson[18] and Hill[17] that the mucosa of the intestine contains sensory fibers and that these lesions represent exuberances of the same fibers (Masson).[4] We will regard the pain and tenderness as mediated by the splanchnic nerves whose receptors we

will hypothetically place in the innermost portions of the appendix (mucosa or submucosa). Our purpose is to eliminate all other factors which might be accomplices to, or actual agents in, the production of symptoms.

Material and Methods.—One hundred forty-three appendices showing neuromatous lesions and some degree of obliteration, encountered among the routine surgical specimens over a period of two years, were investigated. Because of the high incidence of neuromatous lesions in appendices showing some degree of obliteration, this study deals with such appendices. The organs were fixed in 4 per cent formalin, and paraffin sections from the base, midportion, and tip were stained with hematoxylin and eosin, and by the van Gieson, and the Masson trichrome silver stains. Of these appendices, 81 were removed with the preoperative diagnosis of appendicitis, 62 were removed simultaneously with gallbladders or female genital viscera. The vast majority of the lesions observed were argentaffin neuromata, instances of neuromuscular hyperplasia being relatively infrequent.

Conscious of the fact that failure to demonstrate the presence of neuromatous lesions may be the result of inadequate examination, but recalling that according to Masson[4] these nervous lesions may be ephemeral, as a control 36 appendices showing no neuromatous lesions and some degree of obliteration were investigated for their comparative value with appendices showing nervous lesions.

The clinical histories of all cases were analyzed with special attention to types of discomfort complained of, physical and laboratory findings, histories suggestive of previous discrete appendicular attacks and actual operative findings.

A short histologic description of the neuromatous lesions encountered in these 143 appendices shall be given. This is followed by a tabulated analysis of the histories of the various patients, whose appendices did or did not show neuromatous lesions, the histories of the latter being used as controls. An attempt to correlate the clinical and pathologic findings concludes the study. According to whether or not the appendix was the sole cause of the patient's discomfort, the material at our disposal was divided into three groups:

Group I deals with the histories and clinical findings of patients whose appendices, containing neuromatous lesions, were removed with the preoperative diagnosis of appendicitis. Special attention was given to the temperature, leukocyte counts, complaints, histories of previous attacks of appendicitis, and physical and operative findings. Group II deals with the histories and clinical findings of patients whose appendices, likewise removed with the preoperative diagnosis of appendicitis, disclosed no neuromatous lesions. Group III deals with patients having neuromatous lesions in incidental appendices, *i.e.*, appendices removed routinely during cholecystectomy or gynecologic operations.

Pathologic Description.—Lesions varying from mere streaks to diffuse or circumscribed masses of neuromatous tissue measuring up to 1.4 Mm. were encountered in 143 appendices. In a single appendix the varied con-

figurations of the axial lesions could be demonstrated. Thus one segment revealed the negligible lumen reduced to a small slit containing cellular detritus. The fragments of epithelium of opposing sides and three crypts were surrounded by masses of lymphocytes peripherally in distinct follicle arrangement. Lymphoid elements composed the mass of tissue between residual epithelium and peripheral submucosa. In a subsequent segment lumen and epithelium were absent. At the axis of a generally fatty submucosa were distinct or fusing nodes, composed of lacy tissue from which occasional stands penetrated adjacent tissue containing lymphocytes. In sections stained with hematoxylin and eosin, the lace-like tissue was composed of tortuous columns of vacuolated, lightly eosinophilic material, the columns outlined by denser eosinophilic threads. (With the Masson trichrome stain the lacy tissue appeared light, transparent, red or violet, the bordering fibers, dark blue.) Oval or spindle-shaped nuclei with diffusely distributed, fairly dense chromatin were scattered through the tissue generally in contact with the coarser eosinophilic threads. The impression was gained of columns of spongy tissue viewed in cross and tangential section. From the poles of these lesions outspoken strands of tissue emerged. In a third and more distal segment, the impression of strands was magnified by the closer distribution of thick eosinophilic threads, though here too the intervening stroma was vacuolated and outlined by delicate, darker red fibrils. In association with these were sometimes noted argentaffin cells. Argentaffin cells were likewise noted in lesions bordered by lymphocytes. In many cases the disposition of these lymphocytes in separated masses was distinctly reminiscent of the follicles of the mucosa and the submucosa. Other components frequently observed by us as well as by other investigators, were eosinophilic leukocytes. Both these elements are features of the normal mucosa. It seems that the lymphocytes, because of the frequent regularity of their disposition, are generally not evidences of regression of argentaffin neuromata but rather, like the neuromatous tissue, vestiges of the normal mucosa and submucosa.

In a few instances the light-staining elements were delicate columns or strands among which were ganglia cells. For the presence of these we postulate inflammation which, in completely destroying the mucosa or in producing cicatricial contraction in a centripetal direction, thrusts these submucosal structures, possibly irritated to hypertrophy, in a prominent and axial position.

Occasionally a nodule was seen which tinctorially very closely resembled in its constituents the muscularis mucosa, the columns or fibers in these cases being somewhat more compact. In a single instance the unobliterated segment disclosed a proliferation of muscularis mucosa with apparent extension into the mucosa. In the obliterated segment of another appendix, a circumscribed lesion measuring 0.45 Mm. adjoined a cluster of lymphocytes. Though tinctorially somewhat lighter yellow, in sections stained by the van Gieson method, this lesion morphologically resembled the muscularis mucosa. In an unobliterated segment of the same appendix, the muscularis mucosa definitely and contrastingly bordered hyperplastic mucosal nerve elements. Throughout

the section nervous and muscular hyperplasia was observed, the nervous tissue being very conspicuous in the mucosa. The above represents the slightly varied pictures, exclusive of pure scar and granulation tissue, which we observed.

From this short outline it may be inferred that the structures described may be nervous elements. In morphology they strongly resembled the mucosal mesh. From our material it appears that the nerve tissue present in the center of obliterated appendices, just as the lymphocytes and lymph follicles which were often encountered, is an apparent vestige of elements normally present in the mucosa and submucosa of the appendix.

GROUP I

HISTORIES AND PHYSICAL FINDINGS IN PATIENTS WHOSE APPENDICES, CONTAINING NEUROMATA, WERE REMOVED WITH THE PREOPERATIVE DIAGNOSIS OF APPENDICITIS

Table I is included to show the pertinent data, particularly evidences of pain, tenderness, *etc.*, which could perhaps be interpreted as the result of neuromata.

Operative Pathology.—The following are the pertinent features found at operation for removal of appendices which contained the neuromatous lesions and no evidence of inflammation.

Of the 51 partially obliterated appendices, 30 were kinked or adherent to neighboring viscera, 13 were fibrotic or atrophic but showed no peritoneal adhesions or inflammation. Eight were associated with other pathologic findings such as sliding inguinal hernia, marked retroversion of the uterus, distended cecum or hyperperistaltic ileum, mesenteric lymphadenitis, perisalpingitis, ruptured peptic ulcer, large ovarian cysts, and abscess of the liver.

Of the 13 patients showing no peritoneal adhesions, in whose appendices, according to our standards of elimination, neurogenic lesions would be acceptable as the etiologic element in the production of symptoms, one patient had, in addition to appendiceal symptoms, multiple complaints such as headache, constipation and arthritis. Another was operated upon during an attack similar to one experienced six months previously; a third during one of multiple attacks, some associated with fever and the first occurring two years previously. Three described multiple attacks associated with only appendiceal pain. Two described attacks associated with episodes of diarrhea and fever, and one with constipation. One patient complained of a loss of weight attributed to loss of appetite. The pain in another was provoked by hunger and relieved by food. Another, with no history of similar attacks, recalled epigastric distress, experienced one year previously and relieved by soda. The abdominal pain in another was related to menses.

Of the 21 obliterated appendices, eight showed peritoneal adhesions of some degree occasionally producing kinks. Nine were associated with extra-appendiceal alteration. Four disclosed fibrotic changes or were normal. Of the four showing neither peritoneal involvement nor mechanical alteration,

TABLE I

APPENDICES CONTAINING NEUROMATOUS LESIONS

Some of the Pertinent Signs and Symptoms	Number of Patients with a Clinical Diagnosis of					
	Acute Appendicitis	Subacute Appendicitis	Chronic Appendicitis	"Interval" Appendix	"Appendicitis"	Miscellaneous Diagnoses
	17	15	16	23	7	3
Number of patients having pain in epigastrium	1	3	1		1	
Epigastrium and right lower quadrant	8		1	4		
Right lower quadrant	8	12	14	17	4	3
Lower abdomen					1	
Left lower quadrant					1	
Diffuse pain				1		
Number of patients having tenderness in epigastrium	2					
Epigastrium and right lower quadrant				2	2	
Right lower quadrant	13	12	16	12	3	3
Lower abdomen	1					
Left lower quadrant and hypochondrium				1	1	
Diffuse tenderness	1	1		1		
Number of patients having rigidity in right rectus region	9	2		3		1
Number of patients having gastro-intestinal disturbances:						
Nausea	1	3	5	9	2	1
Vomiting						
Nausea and vomiting	3	5		4		
Diarrhea	1	1		2	1	1
Constipation	1			4	1	1
Nausea and diarrhea	1					
Elevation of temperature	16	4	2	3	1	
Increased white blood count	16	7	8	9	2	
Previous attacks	8	9	8	14	3	

Remarks:

Acute Appendicitis:
Five appendices showed histologic evidence of inflammatory lesions
Six appendices associated with extra-appendiceal lesions

Subacute Appendicitis:
One appendix showed histologic evidence of inflammation
Two appendices associated with extra-appendiceal lesions

Chronic Appendicitis:
One appendix showed histologic evidence of inflammation
Three appendices associated with extra-appendiceal lesions

"Interval" Appendix:
Two appendices showed histologic evidence of inflammation
Four appendices associated with extra-appendiceal lesions
Six patients disclosed no tenderness

"Appendicitis":
Two appendices associated with extra-appendiceal lesions

in two patients the pain occurring in attacks was associated with episodes of constipation. Another, with a preoperative diagnosis of acute appendicitis, had a leukocyte count of 16,000, the urine postoperatively containing red blood

cells and occasional white blood cells. The fourth, a diabetic, complained of epigastric pain and belching of nine weeks' duration.

Summary.—Eighty-one patients whose appendices, containing neuromata, were removed with the preoperative diagnosis of appendicitis, disclosed the following:

Protocols revealed that 42 patients had histories of previous discrete attacks, after which discomfort persisted for a period, or gave histories of definite recurrent attacks.

Of the 81 appendices, nine were the seat of inflammation, two showing acute suppurating inflammation, this condition having been diagnosed preoperatively. Two appendices displayed less extensive inflammations: one a catarrhal inflammation, the other a focal suppurating inflammation. Of these one was diagnosed acute appendicitis, the other "interval appendix."

Five showed subacute obliterating, or subacute inflammation in partially obliterated appendices. Two of these showed gross evidence of previous inflammation in the nature of periappendiceal adhesions. Of these five appendices, two were diagnosed preoperatively as acute appendicitis, one as an interval appendix, one as subacute, and the fifth as chronic appendicitis. All the patients gave histories of similar previous attacks. At the time of operation the temperature and leukocyte counts of four patients were normal. The fifth patient, operated upon with the diagnosis of acute appendicitis, had a slightly elevated temperature, a leukocyte count of 12,000, and some rigidity.

Thirty-eight appendices showed periappendiceal adhesions or bands producing kinking or stasis with fecoliths.

Seventeen patients had clinical evidence and operative confirmation of extra-appendiceal lesions.

The appendices of 17 patients were observed to be thickened, fibrotic or normal, with no record of extra-appendiceal involvement or impaction.

The ages of the patients in this group varied between ten and 52 years. Nine were in the second, 38 in the third, 12 in the fourth, 20 in the fifth and two in the sixth decades. Twenty-eight of these patients were men; 53 were women.

From an analysis of the histories and clinical findings, in the absence of any uniformity and specificity of signs or symptoms, it seems clear that the neuromatous elements in all these appendices cannot be made responsible for some of the symptoms and particularly for the pain suffered by these patients. These findings do not substantiate the correctness of the diagnosis "neurogenic appendicitis."

GROUP II

HISTORIES AND PHYSICAL FINDINGS OF PATIENTS WHOSE APPENDICES, CONTAINING NO NEUROMATA, WERE REMOVED WITH THE PREOPERATIVE DIAGNOSIS OF APPENDICITIS

Table II shows the pertinent data, particularly evidences of pain, tenderness, *etc.*, in a series of patients upon whom the clinical diagnosis of appen-

dicitis was made. These appendices showed no neuromata. This group may serve as a control to determine whether or not symptoms and physical findings, particularly in regard to pain and tenderness, differ in patients with and without appendiceal neuromata.

TABLE II

APPENDICES CONTAINING NO NEUROMATOUS LESIONS

Some of the Pertinent Signs and Symptoms	Number of Patients with a Clinical Diagnosis of				
	Acute Appendicitis	Subacute Appendicitis	Chronic Appendicitis	"Interval" Appendix	"Appendicitis"
	9	9	10	4	4
Number of patients having pain in epigastrium and right lower quadrant	2			1	
Right lower quadrant	4	7	7	3	4
Right upper quadrant	1	1	1		
Diffuse pain		1	2		
Number of patients having tenderness in epigastrium and right lower quadrant				1	
Right lower quadrant	7	8	6	3	4
Right upper quadrant			1		
Diffuse tenderness		1	1		
Number of patients having rigidity in right rectus region	4	1	1		
Number of patients having gastro-intestinal disturbances:					
Nausea	1		3		1
Vomiting and diarrhea		1			
Nausea and vomiting	3	2	2		
Diarrhea		2	1		1
Constipation		2	1		1
Elevation of temperature	9	3		1	1
Increased white blood count	9	4	2	1	
Previous attacks	4	7	8	4	

Remarks:

Acute Appendicitis:

Four appendices associated with extra-appendiceal lesions

Subacute Appendicitis:

One appendix associated with extra-appendiceal lesion

Chronic Appendicitis:

One appendix showed histologic evidence of inflammation

Two appendices associated with extra-appendiceal lesion

Operative Pathology.—Of the 36 appendices showing no neuromatous lesions, a partially obliterated appendix was the seat of a subacute inflammation, the temperature and white blood count being normal. Of the 20 partially obliterated appendices showing no inflammatory lesions, in 12, factors were disclosed operatively which on a mechanical basis might have produced the

symptoms complained of. In three instances extra-appendiceal intra-abdominal lesions were disclosed operatively. In five no intra-abdominal or intrinsic appendiceal alteration was detected operatively, other than fibrosis.

Of the latter, three appendices were removed during one of frequent attacks of pain simulating appendiceal colic. The attacks in the fourth patient occurred premenstrually. In the fifth patient appendiceal symptoms were associated with belching and epigastric distress.

Six of 15 obliterated appendices disclosed at operation alterations which may have been responsible, on a mechanical basis, for symptoms. Extra-appendiceal lesions were associated in four instances.

Of the five showing neither intra-abdominal nor appendiceal alteration other than fibrosis, one was associated with postprandial pain and intractable constipation; another with diarrhea associated with emotional upsets; the pain of a third, originally unrelated to foods or evacuation, lately occurred postprandially and was associated with diarrhea; the fourth had recently sustained a deliberate (dietary) weight loss of 50 pounds; the fifth, operated upon with a diagnosis of acute appendicitis, had an elevation of temperature of 0.5° F. and a white blood count of 12,500.

SUMMARY.—Of 36 patients whose appendices, containing no neuromatous lesion, were removed with the preoperative diagnosis of appendicitis, 23 gave histories of previous discrete attacks simulating appendicitis. One appendix was the seat of subacute appendicitis. Eighteen appendices showed peri-appendiceal adhesions. Extra-appendiceal lesions were present in seven instances. Ten appendices were thickened, fibrotic or normal but disclosed no extrinsic lesions. The ages of the patients in this group varied between 11 and 62 years, 30 being evenly distributed in the second, third and fourth decades, six patients being above 41 years of age. Eight patients were men; 28 were women.

From an analysis of this control group, it seems clear that the histories and clinical findings of these patients did not vary greatly from those whose appendices contained neuromata. This fact also makes the diagnosis "neurogenic appendicitis" very questionable.

GROUP III

INCIDENTAL FINDINGS OF NEUROMATOUS LESIONS IN APPENDICES WHICH WERE REMOVED DURING CHOLECYSTECTOMIES, HYSTERECTOMIES, ETC.

This group may be mentioned in passing only. It also may serve as control to show pertinent signs and symptoms obviously related to the main disease, in instances in which the appendices just happened to show neuromata.

Thirty-one appendices with neuromatous lesions accompanied diseased gallbladders. The symptomatology and objective findings in these patients were entirely related to gallbladder disease. The tenderness was largely restricted to the hypochondrium and the right upper quadrant. The neuromatous lesions

varied up to 0.375 Mm. in diameter. Areas in the mucosa of the unobliterated portions frequently contained prominent nervous elements. Of interest is the fact that patients in this group varied in age between 26 and 59, the majority being in the fourth and fifth decades. There were 26 women and five men.

Of 31 appendices containing neuromatous lesions, 21 accompanied large uterine myofibromata, many with adenomyosis. Four accompanied large ovarian tumors, one an inflamed salpinx, one an ectopic pregnancy, and one a ruptured ovarian cyst. Three accompanied wedges of ovarian tissue excised because of multiple follicle cysts. The ages of the patients varied between 13 and 57, 17 being being in the fifth decade, seven in the fourth.

Twenty-three patients had alterations in menses. Seventeen complained of pain usually in the lower abdomen. No tenderness was elicited in 12 instances. A mass was palpated without the production of tenderness in three and with production of tenderness in four patients. Ten patients evidenced tenderness to abdominal or vaginal palpation. Tenderness in the right lower quadrant was elicited in only two patients, one having a tubal pregnancy, the other a recently ruptured ovarian cyst.

Twenty-nine patients were operated upon with a gynecologic diagnosis, two with diagnoses of appendicitis. One of these actually had a ruptured ovarian cyst; the other, a salpingitis.

Discussion.—A rigid analysis of the histories and operative findings in 81 patients whose appendices showed neuromatous lesions and some degree of obliteration, revealed nine appendices to be the seat of inflammation, 17 to be associated with extra-appendiceal lesions and 38 with peritoneal adhesions or bands. Whereas these adhesions did not always involve attachment to the parietal peritoneum or mesentery and irritations of somatic nerves, they definitely introduced a barrier to the proper functioning of the intestine. It is our impression that the symptoms of appendicitis occurring in repeated attacks at varying intervals may primarily have a mechanical basis. The kinking, twisting or fixation of the appendix, by adhesions or bands, may interfere with its property of evacuation. This failure to empty may produce intermittent distention in an already thickened or poorly distensible organ, producing pain without elevation of temperature and leukocytes, a syndrome frequently diagnosed as "chronic appendicitis," or "interval appendicitis." If, however, this failure to empty produces prolonged stasis and possible interference with circulation, an inflammation may supervene. This inflammation may be severe or mild, obviously demanding surgical intervention, or subsiding spontaneously, leaving as evidence more adhesions, further kinking, and denser fibrosis. When the appendix is entirely obliterated, the element of distention in the production of pain is not a consideration. However, there is roentgenologic evidence that periappendiceal adhesions causing a tug on neighboring segments of intestine may alter the normal evacuation of the ileum and probably incite some degree of distress.

Seventeen appendices satisfied our criteria, in that mechanical and ex-

trinsic factors were eliminated. However, comparisons of these with appendices likewise devoid of extrinsic alterations and showing no neuromatous lesions somewhat weakened their significance. Sixty-two appendices removed simultaneously with other organs, the major seat of pathologic changes, and being associated with no, or rare and questionable appendiceal symptoms, disclosed neuromatous lesions of comparable magnitude. The apparently incidental feature of the lesions in these instances and the fact that they occurred at a relatively advanced age further detract from their specificity.

In several well studied cases, fortuitously occurring in physicians or their relatives, neuromatous lesions were encountered in the obliterated portion of acutely inflamed appendices, and histories of multiple very similar, perhaps less severe attacks than that provoking the operation, were obtained. In the course of examination of appendices accompanying other organs, often catarrhal, sometimes focal suppurating inflammation is encountered, actually an accidental finding. That appendicitis of subclinical variety may occur is evidenced by our still high mortality from appendicitis. That relatively benign inflammations occur and subside is manifest by the high percentage of obliteration encountered in age groups incompatible with involutional obliteration of the appendix. However, the presence of the same lesions in older age groups as disclosed by the 62 appendices accompanying diseased gallbladders and internal genital organs, would indicate them to be merely a feature of obliteration.

If the lesions are the sequelae of inflammation, they may be products of precipitous alterations of the mucosa. Inflammation notoriously depletes the lymphoid tissue (Masson[18]), leaving the residual mucosal elements conspicuous. Of these, nerve fibers are a prominent component. Opposing portions of residual mucosa and submucosa at the site of injury fuse and thus we obtain the picture illustrated by many authors of neuromatous lesions of the appendix. Masson stated that neuromata in the state of regression are infiltrated by lymphocytes, and distinguished between infiltrating lymphocytes and persistent follicles. It has been our experience to find large neuromatous lesions bordered or separated by lymphocytes, very frequently in follicle formation; to find infiltrating lymphocyte coextensive with outspoken follicles. We have the impression that the presence of lymphocytes is not a reliable evidence of regression of neuromata and that these cells are most frequently residual elements of the mucosa or submucosa.

The histories of patients with and without neuromatous lesions vary little. Specific characters are lacking, particularly as concerns pain. It is neither more confined to one region, nor more diffuse, neither more nor less severe in those patients with neuromatous lesions in their appendices, than in patients without such appendiceal lesions. This is also true when the appendix shows inflammatory changes in addition to neuromatous lesions. From the histories of the patients with neuromata in their appendices, and from the histories of the control groups, it seems clear that the neuromatous lesions in the appendix

are mere incidental findings, not likely either to cause clinical symptoms or to alter the clinical symptoms of any variety of appendicitis. The term "neurogenic appendicitis," therefore, seems unwarranted.

CONCLUSIONS

The so-called neuromatous lesions occurring in the axis of a considerable percentage of partially or completely obliterated appendices appear to be remnants of mucosa, entangled in obliterating fibrous connective tissue. When noted in young adults, they are perhaps stigmata of previous inflammatory assault upon the mucosa or submucosa.

Appendices containing no neuromatous lesions, used for clinical comparison, disclosed very similar clinical histories and operative findings.

By a process of elimination, only fragmentary evidence of the implication of these in the clinical phenomena of "chronic appendicitis" was obtained.

These neuromatous structures in young individuals might be regarded as evidence of previous attacks of appendicitis, but are certainly of questionable value from a differential clinical diagnostic standpoint.

From the facts at our disposal, it does not seem likely that a clinical diagnosis of neurogenic appendicitis can be made.

BIBLIOGRAPHY

[1] Masson, P.: Les Néromes sympathiques de l'appendicite oblitérante. Lyon Chir., **18**, 281, 1921.

[2] Maresch, R. L.: Über das Vorkommen neuromartiger Bildungen in obliterierten Wurmfortsätzen. Wien. Klin. Wchnschr., **34**, 181, 1921.

[3] Masson, P.: Les Lésions du Plexus Nerveux périglandulaire dans l'appendicite chronique. Bull. et Mém. Soc. Méd. d. Hôp. de Paris, **46**, 956, 1922.

[4] Masson, P.: Carcinoids (Argentaffin Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa. Am. Jour. Path., **4**, 181, 1928.

[5] Urech, E.: L'Appendicite neurogène de Masson. Rev. Méd. de la Suisse Rom., **43**, 425, 1928.

[6] Hosoi, K.: Neuromatosis of the Vermiform Appendix. Arch. Path., **16**, 500, 1933.

[7] Hosoi, K.: Neurogenic Appendicitis. Am. Jour. Surg., **22**, 428, 1933.

[8] Simard, L. C.: On the Frequency of Nervous Lesions of the Vermiform Appendix—"Neuroappendicopthy." Canad. M. A. J., **33**, 518, 1935.

[9] Fein, M. J., Hanan, J. T., and Seidler, V. B.: Plexiform Neuroma of Appendix. Am. Jour. Surg., **39**, 27, 1938.

[10] Llombart, A.: Les Lésions Nerveuses dans les Appendicites Aigues et Chroniques. Ann. d'Anat. Path., **15**, 605, 1938.

[11] Rossle, R.: Beitrag zur Kenntnis der Pathologie der motorischen Apparate des Wurmfortsatzes. Mit. a. d. Grenzgeb. d. Med. u. Chir., **42**, 143, 1930–1932.

[12] Schweizer, P.: Über neuromartige Bildungen in obliterierten Wurmfortsätzen. Schweiz. Med. Wchnschr., **52**, 1202, 1922.

[13] Schack, L.: Der neuromuskuläre Apparat des Wurmfortsatzes bei der sogenannten chronischen Appendicitis. Beitr. z. path. Anat. u. z. allg. Path., **90**, 392, 1932.

[14] Collins, D. C.: Mechanism and Significance of Obliteration of the Lumen of the Vermiform Appendix. ANNALS OF SURGERY, **104**, 199, 1936.

[15] Reiser, K. A.: Der Nervenapparat in Processus Vermiformis nebst einigen Bemerkungen über seine Veränderungen bei chronischer Appendicitis. Ztschr. f. Zellforsch. u. Mikr. Anat., **15**, 761, 1932.

[16] Masson, P.: Neural Proliferation in the Vermiform Appendix. Cytology and Cellular Pathology of the Nervous System. W. Penfield. New York, Hoeber, Inc., **3,** Sec. **25,** 1097, 1932.

[17] Hill, C. J.: A Contribution to Our Knowledge of the Enteric Plexuses. Proc. Roy. Soc. London, Philosophical Transactions, Series B, **215,** 355, 1926–1927.

[18] Masson, P.: Contribution to the Study of the Sympathetic Nerves of the Appendix. The Musculonervous Complex of the Submucosa. Am. Jour. Path., **6,** 217, 1930.

[19] Oshima: Über die Innervation des Darmes. Ztschr. f. Anat. u. Entwcklngsgesch., **90,** 725, 1929.

[20] Ranson, S. W.: Afferent Paths for Visceral Reflexes. Physiol. Rev., **1,** 477, 1921.

[21] Hertz, A. F.: The Sensibility of the Alimentary Canal. Henry Fronde. Hodder & Stoughton, London, Oxford University Press, 1911.

[22] Ryle, J. A.: Visceral Pain and Referred Pain. Lancet, **1,** 895, 1926.

[23] Morley, J.: Abdominal Pain as Exemplified in Acute Appendicitis. Brit. Med. Jour., **1,** 887, 1928.

[24] Kuntz, A.: The Autonomic Nervous System. 2nd ed., Philadelphia, Lea and Febiger, 1934.

[25] Capps, J. A.: An Experimental and Clinical Study of Pain in the Pleura, Pericardium and Peritoneum. New York, Macmillan Company, 1932.

[26] Montandon, A.: Des Erreurs de diagnostic dans l'appendicite, à l'hôpital cantonal de Lausanne. (Suivi de quelques considérations sur l'appendicite neurogène de Masson.) Rev. Méd. de la Suisse Rom., **51,** 570, 1931.

THE INFLUENCE OF THE EXTERNAL SECRETION OF THE PANCREAS ON LIPID METABOLISM*

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It has long been known that in diabetes mellitus a disturbance of the metabolism of both fats and carbohydrates may occur. Because the two phenomena seemed to be interrelated it was not unnatural that, when insulin was discovered, students of the subject rather generally assumed a wholly adequate replacement therapy had been found. That such is not the case, in certain respects at least, was soon noted by Allan, Bowie, Macleod and Robinson[1] (1924). These workers found in completely depancreatized dogs, in which the carbohydrate metabolism was controlled by insulin, that when life was prolonged for a sufficient length of time, a disturbance in lipid metabolism developed which was characterized by the deposition of excessive amounts of fat in the liver. This observation has been amply confirmed from other laboratories.

Much later, in 1937, Kaplan and Chaikoff[2] established that the process is a slow and variable one and that dogs fed a low fat diet plus vitamin and salt supplements usually require at least 16 weeks to insure the consistent finding of a fatty acid content in excess of 14 per cent of the wet weight of the liver.† These authors[3] also noted following pancreatectomy in animals controlled with insulin, that a quite prompt and persistent fall occurs in the blood lipid levels which is most marked for free and esterified cholesterol. Indeed, cholesterol ester was found at times to have disappeared from the blood stream.

It is especially interesting that Allan and his coworkers,[1] after having discovered the fatty liver phenomenon, also found the means for its control. This consists of the administration of raw pancreas. Later, Hershey and Soskin[4] observed that lecithin also is effective, and Best, Ferguson, and Hershey[5] reported that the potent agent in lecithin is choline. Ralli, Flaum, and Banta[6] confirmed the value of lecithin, and noted that when the animal was fed fat, lecithin was less effective than raw pancreas, but that when the diet was low in fat lecithin was somewhat more effective. Then Dragstedt, van Prohaska, and Harms[7] reported that the adequate dose of raw pancreas

* Presented in part before the Third Congress of the Pan-Pacific Surgical Association, Honolulu, T. H., September 15-21, 1939.

This work was aided by grants from the Christine Breon Fund for Medical Research and the Melville Luther Montgomery Donation of the University of California

† The average normal fat content of the liver varies between 3 and 5 per cent of wet weight.

contains far too little choline for the latter to be responsible for the beneficial results obtained. They also noted certain other phenomena which led them to conclude that a new fat-controlling hormone had been discovered. Their observations and reasoning briefly stated are:

(1) Total pancreatectomy in animals maintained with insulin is followed by fatty infiltration of the liver.

(2) Choline and raw pancreas prevent and cure the process, but the effective dose of the latter contains far too little choline for this substance to be the potent agent of the gland.

(3) The effective factor in raw pancreas is not an enzyme carried by the external secretion, since: (a) Exclusion of the pancreatic juice from the intestine either by draining it to the outside through a fistula or by ligating the pancreatic ducts does not cause the disorder; and (b) the feeding of fresh pancreatic juice to the depancreatized dog in amounts of from 100 to 1,000 cc. per 24 hours, for from 24 to 142 days, does not prevent fatty livers from developing.

(4) The effective factor can be isolated by an alcoholic extract of raw pancreas and probably is a hormone.

The hormone hypothesis has not yet been proved, however. Even before the work of Dragstedt, *et al.*,[7a, b] appeared, the literature contained data which are directly opposed to certain of the findings upon which their conclusions are based. Reference is made specifically to the deposition of fat in the liver following the exclusion of the external secretion of the pancreas from the intestine. In 1905, Pflüger[8] observed that when dogs were subjected to subtotal pancreatectomy and to ligation of the pancreatic ducts, a great increase in the liver fat supervened. These data can be criticized on the grounds that the subtotal pancreatectomy may have created an islet tissue insufficiency which was responsible for the fatty livers. Such criticism cannot be applied to the work of Berg and Zucker[9] who reported, in 1931, that when pancreatic juice was drained to the outside by fistula or when the pancreatic ducts were effectively ligated, extensive fatty infiltration of the liver developed. Moreover, careful analysis of the data presented by Dragstedt, *et al.*, suggests that significant changes may have been misinterpreted. They report that three dogs were subjected to duct ligation and kept on a lean meat, whole milk, and bread diet apparently without vitamin supplements and that the animals lost weight rapidly and died in 44, 56, and 83 days, respectively. At autopsy, the pancreas was extensively degenerated, but some acinar tissue, as well as the islets, was preserved. Histologic sections of the liver showed slight fatty infiltration in two cases, but in the third the liver was entirely normal. It is not certain that these authors were justified in passing over the slight lipid infiltration as of no significance, since the time of survival was less than 14 weeks and since it has been shown more recently by Ralli, Rubin, and Present,[10] using chemical analysis, that successful ligation of the pancreatic ducts in three dogs that were observed for from 13 to 15 weeks resulted in fatty changes in the liver of each one

which were indistinguishable from those seen in the completely depancreatized dog. At the time the work of Ralli and her collaborators appeared, Chaikoff, Entenman and I[11a, b, c] were studying the same subject. We confirmed their findings on a larger series of animals. We also made observations on the

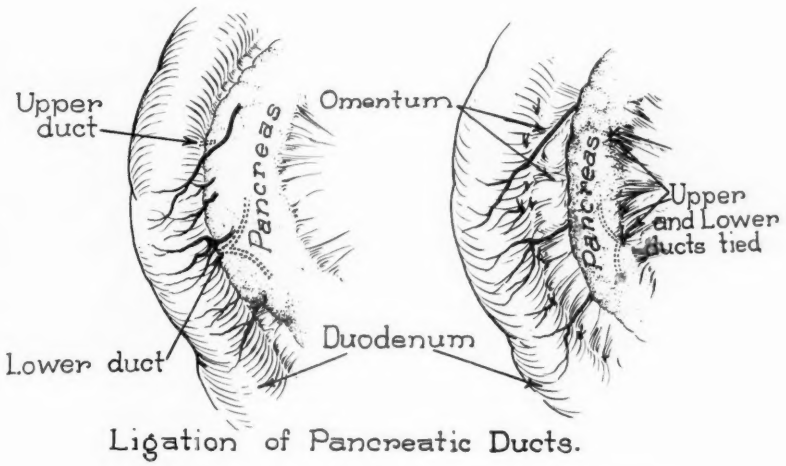

FIG. 1.—Diagrammatic drawing showing the operative procedure.

effect of ligation of the pancreatic ducts upon the blood lipid levels and studied the influence of the feeding of pancreatic juice upon the blood and liver lipids of the depancreatized dog, maintained with insulin, and of the dog subjected to ligation of the pancreatic ducts. Representative portions of the experimental data are presented here in four sections.

EXPERIMENTAL STUDIES

(I) The Effect of Ligation of the Pancreatic Ducts upon Liver and Blood Lipids

Procedure.—The two main pancreatic ducts were doubly ligated and divided between the ligatures. The proximal stumps were then pulled through the gland and tied to the mesentery on the antiduodenal side. All nervous and not definitely identifiable connections between the pancreas and duodenum were severed, including the smaller blood vessels, so that there was no possibility of a ductal communication remaining. Finally, the space between the gland and the duodenum was filled in with omentum which was sutured to the bowel (Fig. 1).

The animals were kept on a low fat, adequate vitamin supplement, and salt mixture diet both before and after the operation and blood samples were taken at frequent intervals. Fasting blood sugars were determined repeatedly upon these animals. With the exception of Dog E20, the values fluctuated between 62 and 92 mg. per cent. Blood sugar levels of from 75 to 82 mg. per cent were found in Dog E20 during the first nine weeks after duct

ligation. A day prior to removal of the liver this dog showed a fasting blood sugar of 127 mg. per cent. The animals were sacrificed after 20 to 24 weeks had elapsed, or earlier if a fatal termination seemed imminent, and the liver and pancreas were examined. The liver was weighed and passed through a meat chopper three times to insure thorough mixing. This procedure was employed to make sure that the sample to be analyzed would reflect the average for the entire liver, since Chaikoff and Kaplan[12] have shown in the depancreatized dog maintained with insulin that the deposition of fat may vary considerably in the different lobes of the same liver. The methods used for analysis have been described elsewhere (for blood[3]; for the liver[13]).

The study was divided into three parts: First, nine animals were fed the basic diet only; second, four animals were given the basic diet and eight units of insulin twice daily; third, six animals were fed the basic diet plus 125 Gm. of raw pancreas twice daily.

Results.—Autopsy showed in the 19 animals that duct ligation had been successful, as represented by atrophy of all recognizable acinar tissue. A variable amount of islet tissue was observed in the different animals. In general, it was considerable and was found chiefly in the proximal or gastric one-third of the pancreas. Some islet nodules also were evident in the distal one-third, while the central one-third was represented by a dense fibrous tissue surrounding the blood vessels which showed no gross evidence of islet structures.

Fatty infiltration of the liver, when present in any sizeable amount, was easily recognized, grossly, by the yellowish, mottled appearance of the peritoneal and cut surfaces of the organ.

Group 1.—Basic Diet Only: The animals were studied for from 12 to 24 weeks, with an average of 18 weeks. All of them lost weight, despite the fact that their appetites were good and that they ingested more food than is usual for animals of their size. Repeated fasting blood sugars were taken and showed a range between 62 and 92 mg. per cent. With only one exception the liver cholesterol and fatty acids showed marked elevations above the normal. The fatty acids ranged between 11.4 and 35.5 per cent, compared with the normal of from 3 to 5 per cent. The one exception (Dog E23) had a high cholesterol content (0.51 per cent compared with normal of 0.25 per cent), but a relatively normal fatty acid figure of only 2.67 per cent (Table I). The reasons for this variation are not clear, although time may have been a factor, since the animal was sacrificed 13.5 weeks after operation. On the other hand, the blood lipid changes in this animal were not different from those observed in the other animals.

The blood lipid findings were rather variable, but in general they showed a distinct fall in all lipid constituents with the drop in esterified cholesterol being the most marked. Thus, the blood and liver lipid changes in the duct-ligated animal correspond with those found by Chaikoff and Kaplan[3,13] in the completely depancreatized dog maintained with insulin.

Group 2.—Basic Diet Plus Eight Units of Insulin Twice Daily: Three animals were studied for 20 weeks and one for 16 weeks. Their appetites

TABLE I

BLOOD AND LIVER LIPIDS OF DUCT-LIGATED DOGS, MAINTAINED ON A LEAN MEAT DIET (WITH OR WITHOUT SUCROSE)*

Dog No.	Period after Duct Ligation†	Weight	Blood Lipids: Cholesterol Total	Cholesterol Free	Cholesterol Ester	Total Fatty Acids	Phospholipid	Total Lipid	Residual Fatty Acids	Period Maintained after Duct Ligation	Liver Weight	Liver Lipids: Total Cholesterol	Total Fatty Acids	Phospholipids	Diet‡ Lean Meat	Diet‡ Sucrose	Condition, End of Period of Observation§
	Weeks	Kg.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Wks.	Gm.	Per Cent	Per Cent	Per Cent	Gm.	Gm.	
E7	Before (0)	11.6	No studies made							24	360	0.41	11.4	1.75	165	35	Thin
	24	8.0															
E9	Before (0)	9.0	No studies made							23	310	0.62	13.5	2.04	135	27	Weak and emaciated
	23	5.8															
E12	Before (0)	9.8	156	136	20	482	350	638	232								
	7.5	8.4	88	88	0	243	195	331	112	21	370	0.66	29.0	1.41	250	50	Good nutritional state
	15	8.4	111	82	29	173	170	284	38								
	18	8.9	111	109	2	284	252	395	114								
E13	Before (0)	11.2	138	107	31	388	360	526	124								
	11	10.5	78	78	0	234	226	312	83	14.5	290	0.41	11.5	2.04	250	50	Weak
	14	10.5	129	110	19	235	227	364	69								
E20	Before (4)	11.5	170	125	45	400	350	570	132								
	Before (0)	11.5	177	131	46	392	330	569	136								
	6.5	9.2	114	113	1	214	203	328	77	12	510	0.32	35.5	1.93	305		Very weak and emaciated
	10	7.0	81	71	10	210	187	291	78								
	12	6.6	94	82	12	225	169	319	103								
E23	Before (8)	15.2	156	132	24	380	335	536	138								
	Before (0)	15.3	149	122	27	362	330	511	120								
	5.5	10.1	138	113	25	383	316	521	153								
	13	6.7	82	84	0	261	232	343	106	13.5	140	0.51	2.67	2.48	350		Very weak and emaciated
	13.5	6.7	85	75	10	246	195	331	108								
E29	Before (4)	10.5	170	142	28	410	400	580	121								
	Before (0)	10.5	164	138	26	407	402	571	118								
	2	9.1	145	126	19	318	282	463	115								
	5	8.8	125	125	0	361	292	471	165								
	14	8.5	145	141	4	264	280	409	73								
	17	8.4	115	119	0	272	242	387	110	18.5	220	0.31	17.7	2.06	282		Good condition
E31	Before (0)	15.8	177	142	35	522	398	699	229								
	2	14.4	135	120	15	315	302	450	102								
	5	12.8	113	112	1	210	234	414	52								
	14	10.3	101	101	0	266	212	367	124								
	16	9.3	117	109	8	270	204	387	127	18.5	300	0.42	20.6	1.79	362		Very weak at end
	18	8.1	98	100	0	292	224	390	142								
E34	Before (0)	11.1	193	141	52	351	416	544	34								
	4.5	8.0	118	118	0	262	265	380	84								
	12	6.8	90	66	24	193	183	283	53								
	15.5	5.1	110	94	16	340	260	450	154	16	255	0.36	19.6	1.84	295		Extremely weak and emaciated
	16	5.0	130	83	47	313	260	443	105								

* Completeness of ligation of ducts confirmed at necropsy.

† The figures in parentheses show the number of days prior to duct ligation when preoperative bloods were taken. Preoperation diets in Tables I to III consisted of 30 Gm. of lean meat per kilo, 6 Gm. of sucrose per kilo per day, with the addition of vitamin and salt supplements.

‡ Constituents, in amounts recorded, were fed twice daily after duct ligation, at 8 A.M. and 4 P.M. Vitamin supplements were added either daily or twice weekly. Two Gm. of Cowgill's salt mixture were added daily.

§ All the dogs had good appetites throughout the period of observation.

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TABLE II

BLOOD AND LIVER LIPIDS OF DUCT-LIGATED DOGS; MAINTAINED WITH INSULIN AND LEAN MEAT-SUCROSE DIET*

Dog No.†	Period after Duct Ligation‡	Weight	Blood Lipids							Period Maintained after Duct Ligation	Liver Weight	Liver Lipids		
			Cholesterol			Total Fatty Acids	Phospho-lipid	Total Lipid	Residual Fatty Acids			Total Choles-terol	Total Fatty Acids	Phospho-lipids
	Weeks	Kg.	Total Mg. per 100 cc.	Free Mg. per 100 cc.	Ester Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Wks.	Gm.	Per Cent	Per Cent	Per Cent
E21	Before (7)‡	5.0	190	135	55	348	325	538	91					
	Before (0)	5.0	188	130	58	322	300	510	79					
	6	5.7	124	122	2	289	250	413	121					
	13	6.5	132	132	0	304	258	436	131					
	18.5	6.9	137	136	1	400	309	537	192					
	19	6.7	131	119	12	306		437		20	255	0.28	14.7	1.60
E22	Before (7)	5.0	190	137	53	440	400	630	133					
	Before (0)	5.0	192	141	51	438	392	630	139					
	6	5.3	134	118	16	326	296	460	116					
	13	5.5	135	137	0	358	300	443	157					
	18.5	5.6	122	121	1	291	280	413	102					
	19	5.6	111	111	0	295	230	406	141	20	275	0.39	20.4	1.69
E25	Before (0)	9.0	173	129	44	389	222	562	208					
	5	8.1	128	134	0	420	261	548	245					
	12	8.0	132	134	0	345	351	477	109					
	17.5	7.5	145	144	1	370	300	515	168					
	18	7.6	126	122	4	334	238	460	172	20	185	0.32	6.32	1.98
E30	Before (5)	13.5	168	135	33	452	284	620	238					
	Before (0)	13.5	175	140	35	472	300	647	245					
	15	12.5	139	133	6	220	258	359	43					
	16	12.3	142	136	6	230	221	372	78	16	470	1.03	34.2	1.85

* Completeness of ligation of the ducts was confirmed at necropsy. All animals recorded received eight units of insulin twice daily, immediately after the ingestion of the diets; their appetites were good throughout and they were all in good nutritional state during the entire period of observation.

† Dogs E21, E22, and E25 received twice daily 250 Gm. of lean meat, 25 Gm. of sucrose, and 7 Gm. of bone ash after duct ligation. Vitamin supplements were added twice weekly. Dog E30 received the same amounts of lean meat, bone ash, and vitamin supplements but the amount of sucrose fed was varied from 25 to 50 Gm. daily.

‡ The figures in parentheses show the number of days prior to duct ligation that preoperative bloods were taken.

TABLE III

BLOOD AND LIVER LIPIDS OF DUCT-LIGATED DOGS; MAINTAINED ON A LEAN MEAT-RAW PANCREAS DIET*

Dog No.	Period after Duct Ligation†	Weight	Blood Lipids: Cholesterol Total	Cholesterol Free	Cholesterol Ester	Total Fatty Acids	Phospholipid	Total Lipid	Residual Fatty Acids	Period Maintained after Duct Ligation	Liver Weight	Liver Lipids: Total Cholesterol	Total Fatty Acids	Phospholipids	Diet‡: Lean Meat§	Diet‡: Raw Pancreas
	Weeks	Kg.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Wks.	Gm.	Per Cent	Per Cent	Per Cent	Gm.	Gm.
E15	Before (7)†	17.7	185	130	55	370	358	555	90							
	Before (0)	17.7	188	117	71	390	326	578	120							
	8.5	17.4	203	140	63	470	405	673	153							
	13	17.9	187	140	47	546	437	733	219							
	20	17.9	201	159	42	505	484	706	150	20	345	0.24	1.87	1.82	265	125
E17	Before (7)	9.0	210	146	64	422	412	632	99							
	Before (0)	9.0	203	152	51	465	415	608	150							
	8	8.3	198	149	49	460	378	658	171							
	12	8.5	182	156	26	430	427	612	123							
	18.5	8.9	177	154	23	412	412	589	120	20	220	0.25	2.28	2.18	135	125
E19	Before (5)	7.8	175	125	50	432	402	607	125							
	Before (0)	7.8	174	124	50	428	400	612	123							
	6	7.5	206	159	47	480	382	686	190							
	13	8.0	176	139	37	456	374	632	179							
	19	8.5	177	141	36	453	345	630	196	20	220	0.26	3.10	2.71	117	125
E24	Before (7)	10.5	180	148	32	450	380	630	172							
	Before (0)	10.4	177	141	36	421	371	598	146							
	5	11.2	178	136	42	506	339	684	248							
	13	9.5	208	164	44	491	396	699	193							
	19	9.7	170	154	16	412	406	582	128							
	20	10.0	163	152	11	400	394	563	128	20	270	0.27	2.84	2.78	157	125
E28	Before (0)	8.9	140	115	25	342	327	482	105							
	6	8.1	122	112	10	408	—	530	—							
	12	8.1	163	138	25	361	327	524	124							
	18	7.9	130	113	17	366	322	496	138							
	20	8.0	148	140	8	386	310	534	152							
	21	8.3	145	136	9	407	331	552	178	22	270	0.23	2.90	2.55	133	125
E33	Before (0)	14.4														
	20	15.3	No studies made							20	285	0.24	3.49	2.33	215	125

* All dogs were in good nutritional state during period of observation; appetites good throughout. Completeness of ligation of ducts confirmed at necropsy.

† The figures in parentheses show the number of days prior to duct ligation that preoperative blood samples were taken.

‡ The constituents listed were fed twice daily. Vitamin supplements and 2 Gm. of Cowgill's salt mixture were added daily. Each dog received approximately 25 cc. of cod liver oil and 30 cc. of the vitamin B concentrate per week.

§ Amount of lean meat given was based upon initial weight of dog: 30 Gm. of lean meat per kilo per day.

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were good and the volume of food ingested was large. In contrast to Group 1, two of the animals actually gained in weight, while the other two lost only a moderate amount of weight. Three of the four animals had marked increases in the total fatty acids of the liver which ranged between 14.7 and 34.2 per cent. The fourth animal (Dog E25) had a slight but distinct rise in the liver fatty acids above normal (6.32 per cent). The liver weight also was low. The blood lipids of this animal, however, were characteristic of the group. All four dogs showed a distinct tendency for the blood lipid levels to fall below normal. This was most marked for the esterified cholesterol (Table II). The findings were in all respects comparable with those of Group 1.

It is evident, then, that lack of insulin or loss of weight is not responsible for the lipid changes in the blood and liver of the dog subjected to successful permanent obstruction of the pancreatic ducts.

Group 3.—Basic Diet Plus 125 Gm. of Raw Pancreas Twice Daily: Five animals were kept for 20 weeks and one for 22 weeks. Three showed definite increases in weight and three very slight losses as compared with the preoperative level. The liver lipids remained low with fatty acids ranging between 1.87 and 3.49 per cent and total cholesterol between 0.23 and 0.27 per cent. The blood lipids were maintained at normal or near normal levels (Table III).

These findings correspond closely with the results obtained by Chaikoff and Kaplan[14] for the completely depancreatized dog maintained with insulin and fed raw pancreas. They suggest that the blood and liver lipid changes which are demonstrable in the completely depancreatized dog maintained with insulin are due to the exclusion from the body of a substance produced by the acinar tissue or some other element of the pancreas which is removed by pancreatectomy and rendered ineffective by the changes which occur in the gland following successful ligation of the ducts. The recent studies of Montgomery, Entenman, Gibbs, and Chaikoff,[15a] Montgomery, Entenman, Chaikoff, and Nelson,[15b] and Entenman, Montgomery, and Chaikoff[15c] point more directly to the pancreatic juice as the controlling medium. This work showed that the feeding of pancreatic juice to the duct-ligated dog and to the depancreatized dog, maintained with insulin, under the conditions employed, prevents the fatty infiltration of the liver and the fall in blood lipid levels which occur quite uniformly in the untreated controls. The data are summarized briefly in Sections II, III, and IV.

(II) The Effect of the Feeding of Fresh Unactivated Pancreatic Juice upon the Blood Lipid Levels of the Completely Depancreatized Dog Maintained with Insulin

The initial work was undertaken with the idea of determining whether the feeding of pancreatic juice would have an effect upon the blood lipids similar to the administration of raw pancreas.

Procedure.—Pure, unactivated pancreatic juice was collected by means of a modified Elman-McCaughan fistula[16] from dogs which were kept in a good

nutritional state by the feeding of an adequate diet containing vitamin supplements and 30 to 50 Gm. of raw pancreas daily.* The salt losses were controlled by the addition of sodium chloride or sodium bicarbonate to the diet or by the intravenous administration of normal salt or Ringer's solution.

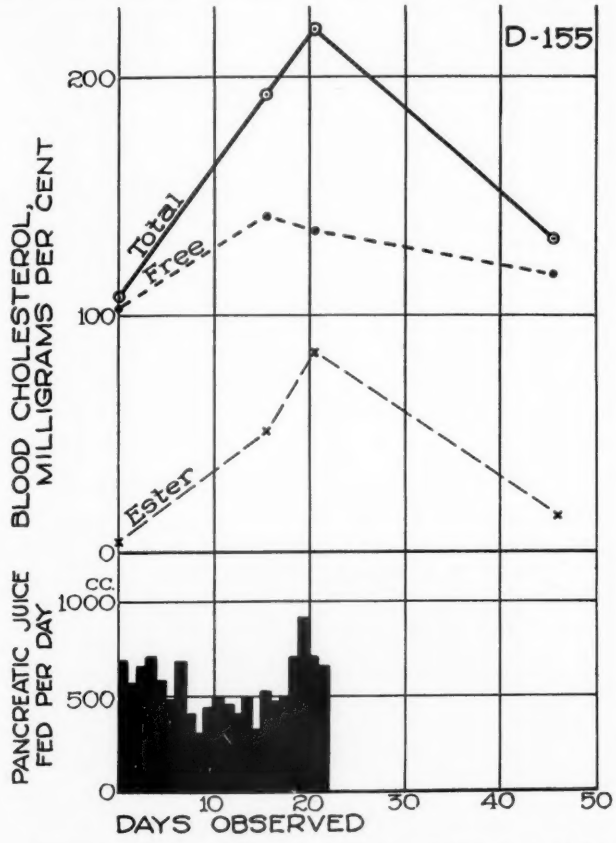

CHART 1.—Showing changes in the blood cholesterol levels of the completely depancreatized dog maintained with insulin, in response to the feeding of fresh, unactivated pancreatic juice.

The fresh juice was then thoroughly mixed with a basic diet consisting of raw lean meat, sucrose, bone ash, and vitamin supplements, and fed to the depancreatized dogs. Feedings, and eight units of insulin were given twice daily. The amount of juice fed ranged between 300 and 900 cc. each 24 hours for a period of three weeks. Fasting blood samples were taken before, during, and after the pancreatic juice feeding period, and were analyzed by the chemical methods previously noted.[3] Four experiments were performed upon three dogs.

Results.—In each experiment the blood lipids showed, initially, the low levels which are characteristic of the depancreatized dog.[3] Feeding of fresh pancreatic juice caused a prompt rise of these levels to or distinctly above normal. Withdrawal of the pancreatic juice resulted in a rapid return of

* The juice producers used in the longer experiments received 100 Gm. of raw pancreas twice daily.

the blood lipids to the initially low levels. The fluctuations were most marked for cholesterol, an example of which taken from one experiment is shown in Chart 1. These findings are quite comparable with the changes in the blood lipid levels of the depancreatized dog which are produced by the ingestion of raw pancreas (Chaikoff and Kaplan[14]).

These initially effective results suggested that the feeding of pancreatic juice over longer periods of time might have a continuing beneficial effect on the blood lipids and a protective action on the liver lipids. Such was found to be the case. Examples of the protective action on the blood lipids are shown in Table IV. The effects of pancreatic juice feeding on liver lipids and the description of the procedures used in both the blood and liver lipid studies are presented in Section III.

(III) The Effect of the Feeding of Unactivated Pancreatic Juice upon the Liver Lipids of the Completely Depancreatized Dog Maintained with Insulin

Procedure.—Five depancreatized dogs were maintained on the basic diet and eight units of insulin, twice daily, as described in Section II. In addition, 125 Gm. of raw pancreas were administered with each meal, by forced feeding when necessary, until a vigorous appetite was reestablished. The raw pancreas was then displaced by unactivated pancreatic juice (Elman-McCaughan fistula) which was fed over a period of 20 weeks. The circumstances required that the juice should be collected in San Francisco and fed in Berkeley. As a result the juice was not strictly fresh. Dogs D228, D229, D230 and D234 received an average of 377 cc. of pancreatic juice each 24 hours in amounts of about 100 to 300 cc. per meal. The mean age of the juice was 16 and 28 hours at the evening and morning feedings respectively. Dog D256 received an average of 420 cc. per day of a juice which had a mean age of five to seven hours at the time of feeding. At the end of the study, the animals were sacrified by the intraperitoneal administration of nembutal. The livers were removed and examined as described by Kaplan and Chaikoff.[13]

Results.—All of the animals were in good spirits and their nutritional condition appeared to be satisfactory, although one had lost considerable weight (Dog D234, liver fatty acids, 3.11 per cent). The livers showed a fatty acid content that ranged from 3.11 and 7.0 per cent, as compared with the fatty acid levels of 14.4 to 29.2 per cent (average 24 per cent) that were found in the livers of 30 controls, depancreatized dogs that were observed in the laboratory for periods of 19.5 to 21 weeks on diets containing no raw pancreas. It is possible the results would have been more favorable if the juice had been fresher, and available in larger amounts (Table V).

(IV) The Effect of the Feeding of Unactivated Pancreatic Juice upon the Blood and Liver Lipids of the Dog Subjected to Successful Ligation of the Pancreatic Ducts

These studies were undertaken as controls on the observations on the depancreatized dog, maintained with insulin, since it had previously been

demonstrated that duct-ligated dogs develop fatty livers and low blood lipid levels in the absence of adequate replacement therapy. Four dogs received an average of 420 cc. of pancreatic juice per 24 hours. Four other dogs were used as untreated controls. The pancreatic juice, when fed, was approximately five to seven hours old. It was obtained from animals prepared and maintained by the methods described in Section III. The juice-fed and control animals were maintained on a lean meat diet plus vitamin and salt supplements and eight units of insulin twice daily. The latter was employed to protect against a possible insulin insufficiency.

Results.—Pancreatic juice was found to exert a protective action on both the blood and liver lipids which is comparable with the beneficial effects of raw pancreas.[15b, c] The controls, with one exception, developed high fatty acid levels in the liver. The exception had a borderline fatty acid content of 7.13 per cent. All control animals showed a fall in the blood lipid levels below the preoperative figures and below the findings in the juice-fed group. The data on liver lipids are shown in Table VI. The protective action on the blood lipid levels is illustrated by data from two dogs in Table VII.

Discussion.—Study of the existing data concerning the influence of ligation of the pancreatic ducts upon lipid metabolism discloses a preponderance of evidence in support of the occurrence of fatty infiltration of the liver following this procedure. The failure of Dragstedt, *et al.*,[7a] to obtain fatty livers cannot be considered as unequivocal evidence against their appearance, outweighing that presented by other laboratories, since it may have been due to the shorter period of survival of their animals. Moreover, a "slight fatty infiltration" of the liver was noted in two of their dogs which, quite possibly, was early evidence of a change that would have become more pronounced if the animals had lived for a longer period of time. Finally, the "normal" liver, found in the third animal, which appears to carry the burden of their belief, may have been due to a short survival period or to the unexplained biologic variation which was responsible for low liver lipids in four of our 21 duct-ligated controls (Dog E23, 2.67 per cent; Dog E25, 6.32 per cent[11b]; Dog E55, 7.60 per cent[18]; and Dog E59, 7.13 per cent[15b]). It would seem, then, that one support for the lipid hormone theory is unfounded.

The existence of the second support, namely that pancreatic juice, when fed, does not prevent the development of a fatty liver in the depancreatized dog maintained with insulin, must now be considered to be extremely doubtful in view of the work of Montgomery, *et al.*,[15a, b, c] which is summarized in Sections III and IV of this paper, and in which it was shown that the administration of 377 to 420 cc. of pancreatic juice per dog per day for 20 weeks kept five depancreatized and four duct-ligated dogs in good nutritional state and prevented the deposition of excessive amounts of fatty acids in their livers. This evidence is most significant because it is positive, since the material fed possessed qualities of effective control in conditions which quite uniformly lead to fatty liver formation in the absence of proper replacement therapy.

The failure of Dragstedt, *et al.*,[7a] to obtain similar results seems, therefore, to have been due to some defect in their methods or materials. It may have been a weakness in the basic regimen, since their depancreatized dogs failed to survive even with insulin replacement therapy, a circumstance which is certainly contrary to our experience. Whether this is due to the apparent lack of vitamin and salt replacements in the diet, or to failure to bring the animals safely through the postpancreatectomy depression period by forced feeding and the use of raw pancreas, whenever these methods were needed, is uncertain. The failure may also have been due, in part at least, to the character and perhaps to the volume of the administered pancreatic juice. Speculation on the latter point is of limited value, since no data were given concerning the average daily dose. Concerning the character of the juice, something more positive can be said. Entenman, Chaikoff, and I (unpublished) observed in the course of the work on the influence of pancreatic juice upon the blood lipid levels in the depancreatized dog maintained with insulin,[11a] that activated pancreatic juice from the Dragstedt, Montgomery, and Ellis[17] fistula gave less consistent results than the unactivated pancreatic juice obtained from the Elman and McCaughan[16] fistula. It was for this reason that juice from the latter type of fistula was used by us in the successful studies on liver lipid control.

TABLE IV

EFFECT OF INGESTION OF PANCREATIC JUICE FOR LONG INTERVALS UPON WHOLE BLOOD LIPIDS OF COMPLETELY DEPANCREATIZED DOGS MAINTAINED WITH INSULIN

Dog No.	Weight	Period After Pancreatectomy	Period Fed Pancreas	Period Receiving Pancreatic Juice	Cholesterol			Total Fatty Acids	Phospholipid	Total Lipid
					Total	Free	Ester			
	Kg.	Wks.	Wks.	Wks.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.
D228	10.5	(1)*			142	128	14	368	315	510
	10.5	(0)			153	138	15	363	313	516
	9.9	5.8	5.8		176	138	37	356	442	531
	9.6	8.0	8.0		198	148	50	452	402	650
	9.2	10.4		1.9	166	94	72	412	336	578
	9.2	12.7		4.2	182	121	61	382	382	564
	9.1	15.4		6.9	151	85	66	308	361	459
	9.5	18.4		9.9	142	85	57	410	327	552
	9.7	19.4		10.9	165	106	59	376	365	541
	9.5	23.7		14.2	157	103	54	422	399	579
	9.5	28.0		20.0	175	110	65	453	400	628
D256	14.2	(2.5)			143	112	31	338	372	481
	14.7	(1)			146	106	40	311	358	457
	13.6	3	3		226	128	98	530	413	756
	13.5	7		4	210	117	93	524	487	734
	14.5	11		8	226	108	118	480	473	706
	14.6	14		11	205	109	96	482	371	687
	14.3	16		13	235	125	110	534	492	769
	13.3	23		20	159	105	54	419	383	578

* The numbers in parentheses refer to the number of weeks *before* pancreatectomy.

In the light of these observations, it appears to be necessary to reappraise the statement of Dragstedt,[19] ". . . it seems important to recognize that the

absence of pancreatic juice from the intestine is relatively unimportant, leading only to a partial impairment in digestion and absorption, whereas the deficiency in the internal secretions, insulin and lipocaic, is incompatible with life." Rather than being proved to be unimportant, the evidence now shows that the exclusion of pancreatic juice from the intestinal tract by duct ligation

TABLE V

LIVER LIPIDS OF DEPANCREATIZED DOGS FED UNACTIVATED PANCREATIC JUICE*

	Weight			Pancreatic Juice		Liver	
Dog No.	Initial Kg.	Final Kg.	Period Depancreatized Weeks	Period Fed Weeks	Amount Daily Avg. Cc.	Wt. Gm.	Fatty Acid Content Per Cent
D228	10.5	9.5	28	20	377	530	3.70
D229	9.9	9.8	28	20	377	540	7.00
D230	10.1	9.0	28	20	377	570	5.79
D234	16.7	11.1	24	20	377	535	3.11
D256	13.6	13.3	23	20	420	470	3.19
			Controls				
D208	12.5	12.5	20			1100	20.40
D209	15.0	7.8	20			500	15.10
D210	10.2	7.7	20			637	20.50

* Insulin maintenance, eight units twice daily.

is followed by blood and liver changes that are similar to, if not identical with, those produced by pancreatectomy, and that the feeding of pancreatic juice to the depancreatized dog, maintained with insulin, results in blood and liver lipid pictures which are indistinguishable from those produced in such animals by the feeding of raw pancreas.

It seems apparent, then, that the surgeon who is called upon to permanently obstruct the external secretory mechanism of the pancreas in the course of the treatment of lesions of this gland must recognize that, if the human pattern follows that of the dog, which seems likely, the procedure will lead to major disturbances of the individual's ability to control his lipid metabolism, which must be rectified by proper replacement therapy if the retention of a healthy condition by the patient is to be assured.

CONCLUSIONS

(1) Successful ligation of the ductal communications between the pancreas and the duodenum leads to atrophy of the pancreatic acinar structures and to alterations in the blood and liver lipids that are apparently comparable, in all respects, with the known blood and liver lipid changes which have been observed in the completely depancreatized dog, maintained with insulin.

(2) Unactivated pancreatic juice fed to the depancreatized dog, maintained with insulin, or to the duct-ligated dog, controls the blood and liver lipids in a manner that is indistinguishable from that which follows the administration of raw pancreas.

(3) The external secretion of the pancreas is thus established as an essential factor in the control of lipid metabolism. The manner of its action is as yet not clearly understood.

(4) The surgeon must recognize, therefore, that the exclusion of pan-

creatic juice from the intestinal tract by operation, infection or ductal obstruction may lead to serious metabolic disturbances which must be corrected by proper replacement therapy if the patient's metabolic balance is to be restored.

TABLE VI

LIVER LIPIDS OF DUCT-LIGATED DOGS FED UNACTIVATED PANCREATIC JUICE*

Dog No.	Weight		Period Since Duct Ligation	Pancreatic Juice		Liver	
	Initial Kg.	Final Kg.	Weeks	Period Fed Weeks	Amount Daily Avg. Cc.	Wt. Gm.	Fatty Acid Content Per Cent
E56	12.1	16.0	23	20	420	350	2.24
E63	15.0	19.7	23	20	420	290	4.90
E65	14.3	17.0	23	20	420	317	4.98
E66	13.0	18.0	24	20	420	372	2.62
			Controls				
E57	10.8	10.7	23			255	31.40
E59	9.2	7.3	23			268	7.13
E54	15.3	9.2	23			550	16.60
E70	14.8	10.5	23			381	22.70

* Dogs received a "prophylactic" dose of eight units of insulin twice daily (see text).

TABLE VII

EFFECT OF INGESTION OF PANCREATIC JUICE ON BLOOD LIPIDS OF DUCT-LIGATED DOGS

Dog No.	Weight	Period After Duct Ligation	Period Fed Pancreas	Period Fed Pancreatic Juice	Cholesterol			Total Fatty Acids	Phospholipid	Total Lipid
					Total	Free	Ester			
	Kg.	Wks.	Wks.	Wks.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.	Mg. per 100 cc.
E56	12.1	(1)*			201	125	76	425	402	626
	12.1	(0)			176	108	68	470	392	646
	12.5	3	3		172	107	65	421	332	593
	13.5	6		3	185	129	56	423	432	608
	14.4	11		8	233	140	93	393	489	626
	14.7	15		12	195	109	86	470	398	665
	15.8	22		19	205	130	75	505	486	710
	16.0	23		20	220	124	96	549	460	769
E63	15.0	(1)			153	116	37	388	460	541
	15.0	(0)			160	114	46	409	417	569
	15.4	3	3		189	122	67	498	384	687
	15.0	7		4	164	127	37	466	441	630
	18.1	11		8	196	141	55	448	382	644
	19.6	22		19	207	124	83	432	474	639
	19.7	23		20	199			473	425	672

* The numbers in parentheses refer to the number of weeks *before* pancreatectomy.

REFERENCES

[1] Allan, F. N., Bowie, D. J., Macleod, J. J. R., and Robinson, W. L.: Brit. Jour. Exp. Path., **5**, 75, 1924.

[2] Kaplan, A., and Chaikoff, I. L.: Jour. Biol. Chem., **119**, 435, 1937.

[3] Chaikoff, I. L., and Kaplan, A.: Jour. Biol. Chem., **106**, 267, 1934.

[4] Hershey, J. M., and Soskin Samuel: Am. Jour. Physiol., **98**, 74, 1931.

[5] Best, C. H., Ferguson, G. C., and Hershey, J. M.: Jour. Physiol., **79**, 94, 1933.

[6] Ralli, Elaine P., Flaum, G., and Banta, R.: Am. Jour. Physiol., **110**, 545, 1935.

[7] van Prohaska, J., Dragstedt, L. R., and Harms, H. P.: Am. Jour. Physiol., **117**, 166, 1936.

[7b] Dragstedt, L. R., van Prohaska, J., and Harms, H. P.: Am. Jour. Physiol., **117**, 175, 1936.
[8] Pflüger, E.: Arch. f. d. ges. Physiol., **108**, 115, 1905.
[9] Berg, B. N., and Zucker, T. F.: Proc. Soc. Exp. Biol. Med., **29**, 68, 1931.
[10] Ralli, Elaine P., Rubin, S. H., and Present, C. H.: Am. Jour. Physiol., **122**, 43, 1938.
[11a] Montgomery, M. L., Entenman, C., and Chaikoff, I. L.: Proc. Soc. Exp. Biol. Med., **40**, 6, 1939.
[11b] Montgomery, M. L., Entenman, C., and Chaikoff, I. L.: Jour. Biol. Chem., **128**, 387, 1939.
[11c] Entenman, C., Chaikoff, I. L., and Montgomery, M. L.: Jour. Biol. Chem., **130**, 121, 1939.
[12] Chaikoff, I. L., Kaplan, A.: Jour. Biol. Chem., **119**, 423, 1937.
[13] Kaplan, A., and Chaikoff, I. L.: Jour. Biol. Chem., **108**, 201, 1935.
[14] Chaikoff, I. L., and Kaplan, A.: Jour. Biol. Chem., **112**, 155, 1935.
[15a] Montgomery, M. L., Entenman, C., Gibbs, G. E., and Chaikoff, I. L.: Proc. Soc. Exp. Biol. Med., **43**, 349, 1940.
[15b] Montgomery, M. L., Entenman, C., Chaikoff, I. L., and Nelson, C.: Jour. Biol. Chem., **137**, 693, 1941.
[15c] Entenman, C., Chaikoff, I. L., and Montgomery, M. L.: Jour. Biol. Chem., **137**, 699, 1941.
[16] Elman, R., and McCaughan, J. M.: Jour. Exp. Med., **45**, 561, 1927.
[17] Dragstedt, L. R., Montgomery, M. L., and Ellis, J. C.: Proc. Soc. Exp. Biol. Med., **28**, 109, 1930.
[18] Entenman, C., Montgomery, M. L., and Chaikoff, I. L.: Jour. Biol. Chem., **135**, 329, 1940.
[19] Dragstedt, L. R.: Annals of Surgery, **110**, 907, 1939.

THE RÔLE OF THE SECOND THORACIC SPINAL SEGMENT IN THE PREGANGLIONIC SYMPATHETIC INNERVATION OF THE HUMAN HAND—SURGICAL IMPLICATIONS

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OPPORTUNITIES permitting accurate observations concerning the rôle played by a single spinal segment in the sympathetic innervation of a portion of the human body are exceedingly limited. Of necessity, our knowledge of segmental sympathetic innervation has been obtained through experiments on lower animals, yet sympathectomies performed upon man often disclose discrepancies between the anatomy of the segmental sympathetic innervation as it exists in lower animals and as it pertains to the human being.

This is illustrated in a recently published difference of opinions concerning the Telford[1] and Smithwick[2] operations for preganglionically denervating the blood vessels of the arm. In these operations, the connections of the first thoracic ganglion with the spinal cord are purposely left intact to avoid destruction of postganglionic fibers and the production of a Horner's syndrome. Kuntz and his associates[3] have demonstrated that in lower animals the first thoracic segment contributes to the sympathetic innervation of the forelimb and, therefore, contend that the Telford and Smithwick operations are anatomically inadequate. However, on the basis of clinical observations, DeTakats,[4] Learmonth,[5] and White[6] support Telford's and Smithwick's conclusions to the effect that, provided they are performed properly, these operations will completely destroy the preganglionic sympathetic innervation of the blood vessels of the human arm.

To denervate the blood vessels of the hand, I prefer the preponderantly preganglionic type of operation in which, through a posterior approach, the second thoracic ganglion, the adjacent portions of the sympathetic trunk, the connections with the second intercostal nerve, and the posterior end of that nerve are resected. Through a peculiar operative error, an opportunity was presented in one of these cases to perform a controlled study on the contibution of the second thoracic spinal segment to the sympathetic innervation of the human hand.

Case Report.—Clinic No. 186, 118: E. C., white, female, age 32, was admitted to the Peripheral Vascular Clinic of Cleveland City Hospital, and gave the following history. Fifteen years previously, at age 17, she noticed, for the first time, that the fingers of both hands would become white and cyanotic on exposure to cold or during an emotional upset. At age 25, eight years later, she developed a progressive atrophic arthritis which resulted in severe deformity and crippling of her hands. In addition, she began to suffer intensely from sensations of coldness and numbness in the deformed digits. These had persisted unabated during the past eight years and she desired relief.

Physical Examination.—Both hands were markedly deformed, the various joints being fixed in distorted positions (Fig. 1). In addition, both hands were deeply cyanotic, markedly cold to the touch, and covered with perspiration. Pulsation was palpable in both radial arteries. There was no ulceration, but there were beginning sclerodermatous changes in the fingers. A Landis test was performed, and the skin temperatures taken

FIG. 1.—Roentgenogram showing chronic arthritis deformans of the hands. The arthritis was associated with a severe vasospasm.

from various points on both hands reached vasodilatation levels ranging between 30.5° and 32° C. Both hands became pink, and the subjective sensations of coldness and numbness disappeared. It was explained to the patient that while a sympathectomy would not influence the arthritic process, it would relieve the sensations of coldness and numbness. She agreed to the operation with this understanding.

Operation.—February, 1939: Under general anesthesia, the posterior end of the right third rib was exposed and resected. The posterior mediastinum was opened, and the posterior end of the second intercostal nerve, the second thoracic ganglion, the adjacent portions of the thoracic sympathetic trunk, and the rami communicantes between the ganglion and the intercostal nerve were resected *en masse*. The ganglion was sent to the pathologist for microscopic examination. The following day the right hand was pink, hot, and dry. Sensations of coldness and numbness had completely disappeared; the left hand remained unaffected. The pathologist reported that a sympathetic ganglion had been resected. Two weeks later, a similar procedure was performed on the left side, the resected ganglion being sent to the pathologist for microscopic examination.

The following day it was evident, from only a cursory inspection, that a complete denervation of the left hand had not been obtained. While the left hand was warmer than it had been prior to the operation, it was distinctly cooler than the right hand, and the palm of the left hand was definitely sweaty. At first it was feared that some structure other than the sympathetic trunk had been removed. However, the pathologist disposed of this contingency by reporting microscopic identification of a sympathetic ganglion. The mystery was not cleared up until some weeks later, when a routine roentgenogram of the chest revealed that a technical error had been made during the second operation. The fourth rib instead of the third rib had been resected (Fig. 2). This meant that the third left thoracic ganglion instead of the second had been removed, and that the second

left thoracic ganglion and its connections with the spinal cord were intact. The bilateral anatomic arrangements resulting therefrom is shown in Figure 3. It is seen that a controlled experiment had accidentally been set up in which any difference in the extent of the sympathetic denervation between the left and right hands would indicate the presence of preganglionic sympathetic fibers emerging from the spinal cord through the ventral root of the left second intercostal nerve.

FIG. 2.—Roentgenogram of the upper thoracic region. Note that the posterior end of the third rib has been resected on the right side, and the posterior end of the fourth rib on the left.

Six months later this difference was measured. At a room temperature of 25° C. skin temperature readings were taken from the palms of both hands and the tips of the fingers (Table I).

TABLE I

SKIN TEMPERATURE READINGS SIX MONTHS POSTOPERATIVE

	Right	Left
Palm:	31.0° C.	28.0° C.
1st finger	31.0° C.	28.0° C.
2nd finger	31.5° C.	27.0° C.
3rd finger	30.5° C.	27.0° C
4th finger	30.0° C.	27.5° C.
5th finger	31.0° C.	28.0° C.

From Table I it is seen that the left hand was distinctly cooler than the right, the difference ranging from 2.5° to 4.5° C. (The patient volunteered the information that while complete subjective relief had been obtained in the right hand, the left hand had not been benefited to the same extent.)

A Landis test was then performed. As has been shown,[7] a rise in the skin temperatures of the extremities in response to warming the body is dependent upon an intact sympathetic nerve supply. Forty minutes after the test had begun the temperatures were as noted in Table II.

From Table II it is seen that while the skin temperatures of the right hand were

TABLE II

TEMPERATURE READINGS 40 MINUTES AFTER BEGINNING OF LANDIS TEST

	Right	Left
Palm:	31.2° C.	32.7° C.
1st finger	30.9° C.	32.8° C.
2nd finger	31.1° C.	32.6° C.
3rd finger	30.3° C.	32.2° C.
4th finger	30.1° C.	33.0° C.
5th finger	30.9° C.	32.3° C.

not affected by warming the body, those of the left hand rose from 4.7° to 5.6° C. (Chart 1). The left hand also perspired during the test while the right hand remained dry.

Sympathectomists differ as to the precise rôle played by the second thoracic spinal segment in the sympathetic innervation of the upper extremity. Gask and Ross[8] state that the connector cells for the preganglionic sympathetic innervation of the arm extend from the fourth spinal segment to the ninth. Livingstone[9] reports that he has obtained complete sympathetic denervation of the upper extremity by resecting only the third thoracic ganglion. White[10] gives the fourth to the eighth spinal segments as certain, with the second and third questionable. Incomplete denervations obtained with the Telford operation, as reported by Simmons and Sheehan[11], have been interpreted by these investigators as being evidence for the existence of preganglionic fibers from the second thoraic segment. Smithwick[12] believes that instances of regeneration following his operation also constitute strong circumstantial evidence for the presence of preganglionic connector cells in the second thoraic spinal segment. In fact, he has modified his operation to include intrathecal division of the roots of the second intercostal nerve to prevent regeneration of preganglionic neurons from this spinal segment. The reported case shows that the second thoraic spinal segment definitely plays an important part in the preganglionic sympathetic innervation of the hand.

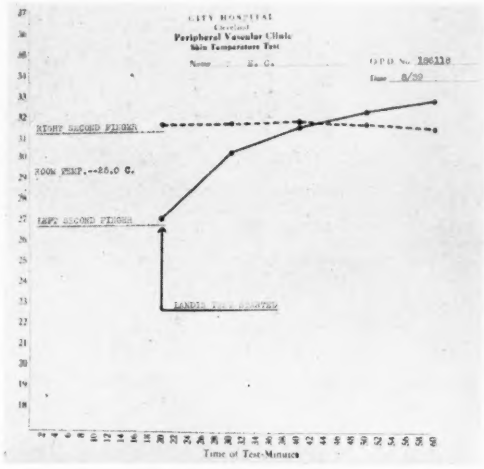

CHART 1.—The chart shows response of skin temperatures of the completely denervated right second finger, and the incompletely denervated left second finger to warming the body (Landis test).

The practical implications of these observations are that any operation designed to preganglionically denervate the blood vessels of an arm must completely destroy all white rami from the second thoraic spinal segment. In every instance, as determined by skin temperature and sweat distribution studies, complete, immediate denervation of the blood vessels and sweat glands of the upper extremity and the cutaneous vessels and sweat glands

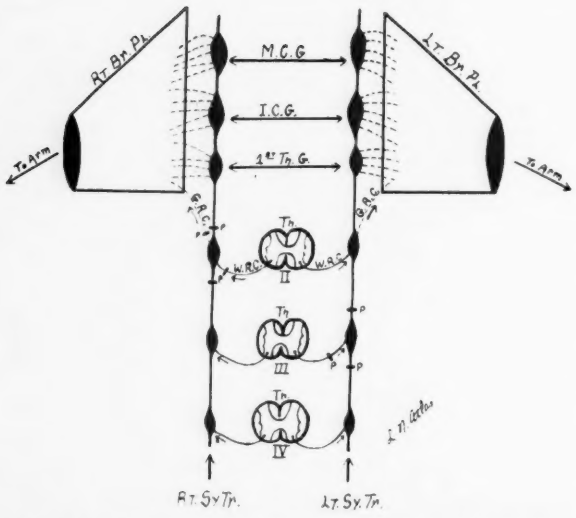

FIG. 3.—A diagrammatic representation of sympathetic innervation of the blood vessels of the hands after resection of the right second and the left third thoracic ganglia and their corresponding rami communicantes.

Rt.—Right; Lt.—Left; Br. Pl.—Brachial plexus; Th. G.—Thoracic ganglia; W.R.C.—Preganglionic rami; Sy. Tr.—Sympathetic ganglionated trunk; M.C.G.—Middle cervical ganglia; I.C.G.—Inferior cervical ganglia; G.R.C.—Postganglionic rami; P.—Points of surgical division. Arrows indicate direction of flow of vasomotor and sudomotor impulses.

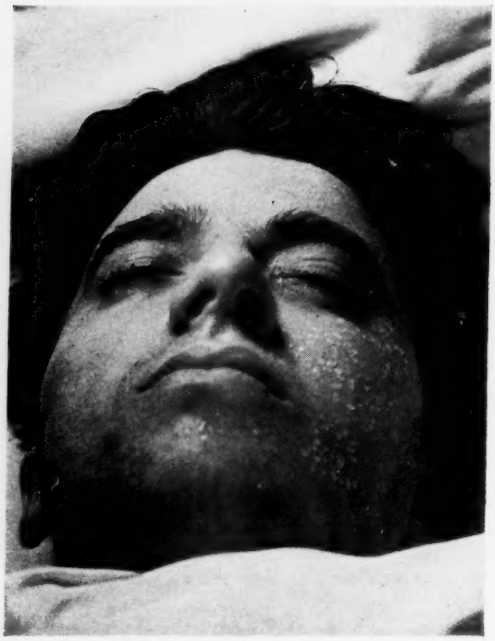

FIG. 4.—Photograph taken shortly after the excision of the right second thoracic ganglion for causalgia of the right hand. Patient received an intravenous infusion. Note the profuse perspiration covering the left side of the face, with complete absence of perspiration on the right side of the face. Perspiration stopped exactly at the midline of face.

of the corresponding half of the face should be obtained (Fig. 4). In none should a Horner's syndrome ensue.

If any adrenalin sensitization has resulted from the destruction of the postganglionic ramus from the second thoracic ganglion to the brachial plexus, it has not been clinically significant in these instances in which the second thoracic ganglion has been resected. It is felt that the Smithwick and Telford operations have both been made needlessly complicated in order to preserve this postganglionic ramus and thereby to achieve a "pure" preganglionic denervation. It appears that this desire to avoid destruction of Kuntz's nerve has also rendered these operations, except when meticulously performed, somewhat uncertain as to the completeness and permanency of the denervation which they effect. I believe that, by and large, excision of the second thoracic ganglion will prove to be essential if disappointing results are to be consistently avoided.

Another conclusion concerns the necessity of resecting the proper rib in a posterior approach to the thoracic sympathetic trunk. The usual procedure, after exposing the thoracic cage by dividing the overlying integument and muscular layers, is to palpate the

first rib and count down. However, the angle between the first rib and the corresponding transverse process is quite sharp (Fig. 2). Unless care is taken to properly identify the first rib by hooking the tip of the exploring finger around its upper edge, it may be missed; in which event the second rib will be mistakenly identified as the first. Latterly, it has been my practice to expose the second thoracic ganglion and its connections by resecting the second rib rather than the third. The exposure thus effected is much more adequate for the necessary manipulations.

REFERENCES

[1] Telford, E. D.: Technic of Sympathectomy. Brit. Jour. Surg., **23,** 448, 1935.

[2] Smithwick, R. W.: Modified Dorsal Sympathectomy for Vascular Spasm of Upper Extremity. ANNALS OF SURGERY, **104,** 339, September, 1936.

[3] Kuntz, Alexander, and Furcolo: Complete Sympathetic Denervation of Upper Extremity. ANNALS OF SURGERY, **107,** 25, January, 1938.

[4] DeTakats, G.: The Effect of Sympathectomy on Peripheral Vascular Disease. Surgery, **2,** 46, July, 1937.

[5] Learmonth, J. R.: Surgery of the Sympathetic Nervous System. Brit. Jour. Surg., **25,** 426, November, 1937.

[6] White, J. C.: Progress in Surgery of Autonomic Nervous System. Surgery, **4,** 781, November, 1938.

[7] Fatheree, T. J., and Allen, E. V.: Observations Concerning the Mechanism of Indirect Vasodilatation Induced by Heat. Arch. Int. Med., **62,** 1015, December, 1938.

[8] Gask, G. E., and Ross, J. P.: Surgery of the Sympathetic Nervous System. 2nd ed. Wm. Wood and Co., 1937.

[9] Livingstone, W. K.: Clinical Aspects of Visceral Neurology. C. C. Thomas, 1935.

[10] White, J. C.: The Autonomic Nervous System. Macmillan Company, 1935.

[11] Simmons and Sheehan: The Cause of Relapse Following Sympathectomy of the Arm. Brit. Jour. Surg., **27,** 234, October, 1939.

[12] Smithwick, R. H.: Problem of Producing Complete and Lasting Denervation of the Upper Extremity by Preganglionic Section. ANNALS OF SURGERY, **112,** 1085, 1940.

JEJUNOSTOMY FOR POSTOPERATIVE FEEDING*

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WE PROPOSE TO DISCUSS the use of jejunostomy with jejunal feeding in upper abdominal surgery, the value of which, we believe, is perhaps not sufficiently appreciated. We feel that this procedure has a definite place in the postoperative management of certain operations and that in some cases it is a life-saving procedure, since it permits the immediate giving of food and fluid to seriously depleted patients.

Jejunostomy has been advocated and has been used for numerous conditions and complications. Some of the indications for jejunostomy which have been advocated[44, 39, 19, 4, 13, 5, 3, *et al.*] are: To nourish a devitalized patient; to feed inoperable cases of cancer of mouth, necks, *etc.*; as a preference to gastrostomy; in extensive duodenal ulcers; in gastrojejunal ulcer, when the patient is too ill to withstand a more extensive operation; in chronic biliary, gastric and duodenal fistulae; for the nausea and vomiting of pregnancy; for pernicious vomiting and inability of stomach to empty itself after operations upon the stomach; in primary resections of small and large bowel; for intestinal obstruction; and in localized and generalized peritonitis. Obviously, jejunostomy was employed in these conditions for but one or two purposes—for feeding to improve the nutrition of a patient either before or after an operation, or to place portions of the gastro-intestinal tract at rest.

In 1885, Gould and Lee[11] reported one of the earliest jejunostomies performed for feeding purposes. Golding-Bird[10] reported a similar procedure in the same year. These patients both died.

Kirschner,[20] in 1929, was the first to make a vigorous plea for jejunostomy in gastric resection cases in order that the patient might be kept in the proper nutritional balance and in order to prevent the "postoperative atony of the stomach" which not infrequently follows gastric resection. He stressed the fact that many gastric resections are performed upon elderly or devitalized patients who do not tolerate further starvation postoperatively. In 1929, he had employed the procedure in 60 cases with good results. Wolfer[44] has given a very good review of the whole subject of jejunostomy with jejunal alimentation.

The Importance of Adequate Nutrition in the Treatment of Surgical Patients.—Malnutrition in the surgical patient is more widespread than is commonly believed, and we are coming to recognize that even those patients

* Read before the Fifty-third Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 11, 12, 1940.

who appear to be normal may be nutritionally depleted. Minot[30] observes that: "The major problems of nutrition do not concern clean-cut deficiency diseases, but the prevention of partial deficiency. Border-line states of nutritional instability are much more common than is usually appreciated. There is a wide zone between optimal nutrition and the level at which classic symptoms of recognized deficiency states develop." Since a variety of complications following operations on the gastro-intestinal and biliary tracts have been shown to be the result of prolonged nutritional disturbances, the nutrition of the patient has become of prime importance to the surgeon.

Jones and Eaton[16] were the first to call attention to the hazards of hypoproteinemia in patients subjected to operations. Jones and his colleagues[16, 17] had their observations corroborated and extended by Ravdin and his coworkers[28, 38, 36, 33] who have stressed the importance of hypoproteinemia and nutritional edema in operations upon the gastro-intestinal tract.

There are several causes for latent or manifest edema in surgical patients. They are: Nitrogen starvation; general malnutrition; purulent and serous drainage; hemorrhage; severe diarrhea; administration of large amounts of sodium salts; increased metabolic demands associated with fever and sepsis; and retention of base due to temporary disturbance of renal function. In the past there has been much emphasis on the salt and water requirements of the surgical patient and very little thought of the protein requirements. It has long been known that the plasma proteins play an important rôle in keeping fluids in the blood vessels, but only recently has it been realized that the proper control of fluids and electrolyte balance in a patient must take into consideration the plasma protein concentration. It is known that excessive amounts of sodium chloride will produce a subcutaneous edema, particularly in the presence of hypoproteinemia, and, therefore, parenteral fluids must be used judiciously. However, it is the concensus of opinion of various investigators that low plasma proteins account for the major part of the edema. It is likewise believed that the low plasma protein is due mainly to an inadequate intake of protein before and after operation.

What are the methods available to combat an hypoproteinemia and the consequent edema? Transfusions of whole blood or serum are very helpful in restoring plasma protein in an hypoproteinemia patient, but these are only temporary aids because the basic problem is one of protein regeneration. Intravenous administration of amino-acid products and lyophiled serum are, admittedly, not yet efficacious in restoring plasma proteins.[33] A restriction of the intake of sodium chloride is important in preventing edema, particularly in patients with lowered plasma proteins. A high protein intake, however, is the one method we have for a permanent restoration of plasma proteins. We believe, with others,[16, 33] that low plasma proteins in surgical patients are due, in most part, to a reduction in the intake of protein *before and after* operation. Since the alimentary tract is still the best route to supply the necessary elements for protein regeneration, and thereby cause a permanent increase in the plasma proteins, we feel that jejunal alimentation is the best

method to employ when the nature of the disease, or the operation, prevents any intake by mouth, for several days.

During the past few years, it has become increasingly obvious that the vitamins play a very important and necessary rôle in the proper nutrition and well-being of an individual. There is ample evidence now that many people live in a chronic state of vitamin deficiency, due to an insufficient or unbalanced diet. A considerable number of patients with gastro-intestinal lesions have for some time prior to admission to the hospital received an inadequate nutrition, more particularly when anorexia, vomiting and pain are present, and some of them have a subclinical or clinical deficiency of certain of the vitamins. Fortunately, the effects of a vitamin deficiency can be corrected quite promptly.

Vitamin A provides for a healthy epithelial structure and, therefore, is one factor in the prevention of postoperative bronchitis, pneumonia and urinary tract infections. The vitamin B complex is important for the proper function of the gastro-intestinal tract. Ravdin *et al.*[33] have demonstrated that a vitamin B deficiency prolongs the emptying time of the stomach. The lack of intercellular cement in vitamin C deficiency is one of the causative factors in wound disruption[22, 37] and subcutaneous edema. One need only note the edema, hemorrhages and poor healing of a patient with scurvy to find proof for this statement. The use of vitamin K in raising the prothrombin level of the blood is now well-established.

There is theoretical, experimental and clinical evidence that a sufficient protein and vitamin intake will lessen the chance of postoperative infections; will lessen the amount of edema in the operative area; will give a better and firmer healing of wounds; will permit a more normal function of the gastro-intestinal tract; and smoother postoperative convalescence. Therefore, we feel that it is most important to immediately correct these nutritive deficiencies preoperatively if the patient is able to take food by mouth and to continue a diet rich in proteins and vitamins postoperatively by means of jejunal alimentation.

Types of Food for Jejunal Alimentation.—The pabulum suggested by Scott, Ivy and Holinger[34, 35] is undoubtedly a good one when prolonged or permanent jejunal alimentation is to be carried out. However, we have found that a simple formula is entirely satisfactory for complementary feedings during the postoperative period after upper abdominal surgical procedures. We have used the following formula with consistently good results—500 cc. milk (peptonized*), one egg, 6 mg. thiamin chloride, 15 cc. vitamin B complex syrup, 300 mg. cevitamic acid, and three drops of Haliver oil with Viosterol. This amount of the formula yields approximately 380 calories. In the last few cases, we have used skimmed milk, thereby eliminating practically all of the fat from the pabulum, and there have been no cases experiencing diarrhea, as did a few when whole milk was used. The milk and well-beaten eggs are peptonized and then the vitamin concentrates are added. It may be administered by a simple "drip" apparatus.

* Peptone from Fairchild Bros. & Foster, New York, N. Y.

The jejunal feedings are started 12 to 24 hours after the patient has been returned from the operating room. Only 200-300 cc. of the pabulum is taken from the refrigerator and placed into the flask of the drip apparatus at one time. At first, the pabulum is allowed to drip so that about 50 cc. is introduced into the jejunum each hour, in order that the jejunum may become accustomed to the feedings. The pabulum is too thick to "drip" like parenteral fluid and it requires the attention of a nurse occasionally to see that it is running in at the proper speed. Gradually, during the next 24-48 hours, the amount of pabulum allowed to run in is increased to 100 cc. per hour, and this is continued day and night. Naturally, the amount of pabulum and the rapidity with which it can be introduced will vary with the individual tolerance for the jejunal feedings. No set rule can be used for all cases. We try to introduce 2,000-3,000 cc. of pabulum over the 24-hour period after the second or third postoperative day. Unless the pabulum is introduced slowly the patient will have abdominal distress and he may experience nausea, vomiting or diarrhea; the latter may be controlled by the addition of small doses of paregoric to the feeding.

For the first two or three days after operation, aspiration of the stomach is carried out at 12-hour intervals. If there is any significant amount of upper gastro-intestinal secretions obtained by aspiration, these important juices are placed in the jejunal feedings, so that the patient will have the use of these vital elements which would otherwise be denied him. Vitamin K concentrates and iron products are added to the feedings when these are indicated. Also, we have used the pabulum as a means of giving codeine, aspirin and the barbiturates for analgesia and sedation, and we believe the patients experienced a more comfortable postoperative course with this method of sedation. The lack of thirst and hunger with this method of feeding added to the smoothness of the patients' convalescence. In all cases, we wait until at least the twelfth postoperative day, so that a definite fistula will have been established before we remove the tube.

Indications.—Jejunostomy, as a complementary procedure, should be considered in the following situations:

I. GASTRIC OPERATIONS

(1) Total gastrectomy.
(2) Subtotal gastrectomy.
(3) Posterior gastro-enterostomy.
(4) Gastroduodenostomy.
(5) Resection of gastrojejunocolic fistula.

Anyone who has had much experience with gastric surgery has had cases in which the stomach would not empty itself properly following operation. This has been called the "vicious cycle of vomiting," "postoperative atony of the stomach," and "postoperative gastric retention." A poorly functioning gastro-enteric anastomosis renders convalescence longer, and unpleasant, because of vomiting and possibly produces a critical state.

The recognized causes of edema in and around a gastro-enteric stoma are:

(a) *Inflammatory.*—This is more pronounced in the carcinomatous gastric ulcer, where there is apt to be little or no free HCl present, and there is likely to be some infection, with its consequent edema at the site of the anastomotic stoma.

(b) *Low Plasma Protein.*—Due to an inadequate intake of protein preoperatively, on account of digestive symptoms occasioned by the disease, patients undergoing gastric operations are prone to have low plasma proteins. The low plasma protein is lowered further by the pre- and postoperative administration of parenteral fluids and by the enforced postoperative period of protein starvation on account of the nature of the operative procedure. Ravdin *et al.*[28, 33] have demonstrated a delay in the gastric emptying time in hypoproteinemic patients and animals before and after operations upon the stomach.

(c) *Low Vitamin C Level in Body.*—When there is inadequate vitamin C, there is loss of intercellular cement in the walls of the small blood vessels, which allows the plasma proteins to escape from the vessels in an abnormal amount, and thereby causes edema of the tissues.

(d) *Too Much Sodium Chloride.*—One can observe edema of the subcutaneous tissues when an excessive amount of saline has been administered, and this evident edema is an external sign of a generalized process taking place throughout the body.

(e) *Operative Trauma.*—Trauma, as a result of the operative procedure, is a recognized cause of local edema in any area of the body.

It appears that continuous jejunal feedings of high protein and vitamin content will reduce the edema of the operative area to a minimum.

Abbott and Rawson[1] have devised a double-lumen tube which is passed through the stomach and into the jejunum *via* the gastrojejunostomy stoma at the time of operation. By this tube, food can be introduced into the jejunum and, at the same time, the stomach can be kept empty by suction through the other lumen of the tube. Ravdin[33, 36] is an advocate for this type of tube for feeding patients following gastric operations by what he calls the "orojejunal" method. We have employed this tube on one occasion without any untoward results, but we are cognizant of some disadvantages connected with its use. It is rather uncomfortable to the patient after two or three days, and he is apt to have considerable discomfort in the nose and pharynx from irritation. Also, should the patient vomit and dislodge the distal end of the tube, or should he pull it out, it cannot be reinserted. We, at present, prefer jejunostomy to the Abbott-Rawson tube for postoperative feeding of extensive stomach operations.

II. SURGERY OF THE BILIARY TRACT

(1) Cholecystogastrostomy.

(2) Hepaticoduodenostomy.

(3) Repair of common duct strictures.

Lesions requiring the foregoing operations are apt to be associated with debilitation from an inadequate food intake, from jaundice, and from loss of bile. Jejunal alimentation, postoperatively, puts the stomach and duodenum at rest and thereby creates an environment more conducive to firm healing of the operative procedures.

III. ANY EXTENSIVE UPPER ABDOMINAL OPERATION

In any operation in the upper abdominal area after which the patient will not be able to take food by mouth for several days, jejunal alimentation offers an ideal way of maintaining the proper nutritive status of the patient. This is particularly important if the patient is debilitated on account of his lesion and on account of an inadequate food intake prior to the operation, as in a gastro-jejunocolic fistula.

Table I gives a list of 14 recent, consecutive cases in which we have employed jejunostomy for postoperative feeding purposes, because we felt that these patients had been on an inadequate diet for some time prior to their operation, or that their operative procedures warranted postoperative jejunal feeding in order that their recovery would be smoother and shorter. There was no mortality in these cases.

TABLE I

FOURTEEN OPERATIONS PLUS COMPLEMENTARY JEJUNOSTOMY

Diagnosis	Operation	Days in Hospital After Operation
1. Carcinoma of stomach	Total gastrectomy	16
2. Carcinoma of stomach	Total gastrectomy	19
3. Chronic duodenal ulcer	Subtotal gastrectomy	16
4. Carcinoma of stomach	Subtotal gastrectomy	20
5. Stricture of common duct	Hepaticoduodenostomy	17
6. Gastric ulcer	Subtotal gastrectomy	17
7. Chronic duodenal ulcer, with pyloric obstruction	Gastroduodenostomy	19
8. Carcinoma of pancreas	Cholecystogastrostomy	14
9. Carcinoma of jejunum	Posterior gastro-enterostomy	18
10. Gastric ulcer	Subtotal gastrectomy (Had postoperative lung abscess and osteomyelitis of sacrum.)	59
11. Carcinoma and polyposis of stomach; angina pectoris	Subtotal gastrectomy	20
12. Gastrojejunocolic fistula	Resection of gastrojejunocolic fistula	15
13. Chronic duodenal ulcer, with pyloric obstruction of three weeks' duration	Posterior gastro-enterostomy	20
14. Chronic duodenal ulcer	Subtotal gastrectomy	25

Technic of Jejunostomy.—We have employed the simplest technic[4] in performing jejunostomy. The four illustrations (Figs. 1, 2, 3 and 4) with their legends make this sufficiently clear so that further description in this text seems unnecessary.

This method of performing jejunostomy is a combination of steps selected from various more complicated procedures advocated by others. It is an adaptation of the Stamm gastrostomy, which Hofmeister,[14] in 1905, recommended for use on the intestines. Long,[24] Mayo,[26] Clue,[4] and others, have written about, and have advocated this type of enterostomy.

This technic has given us very gratifying results. It is very simple, with small chance for a technical error. It requires only two to four minutes to perform, and, therefore, does not add materially to the time or to the scope of the primary operation. The omentum prevents any leakage around the catheter

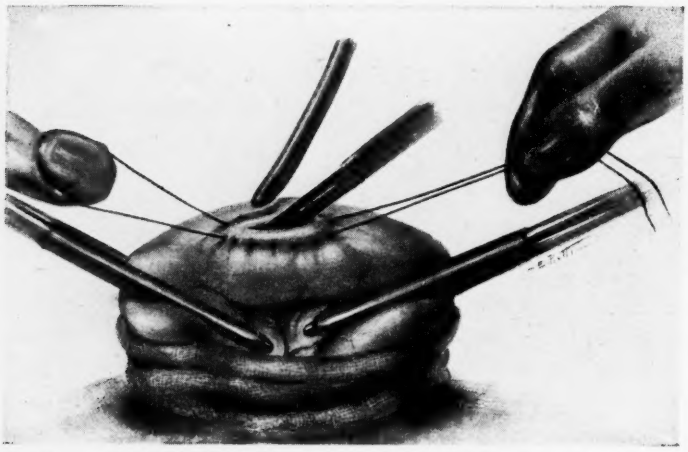

FIG. 1.—A loop of jejunum, 20 or 30 cm. away from the ligament of Treitz, is isolated with intestinal clamps. A double-eyed catheter is led through adjacent omentum. A purse-string suture is placed in the intestine and a stab opening made inside it. The catheter is placed in the bowel pointing distally, and the purse-string tied about it.

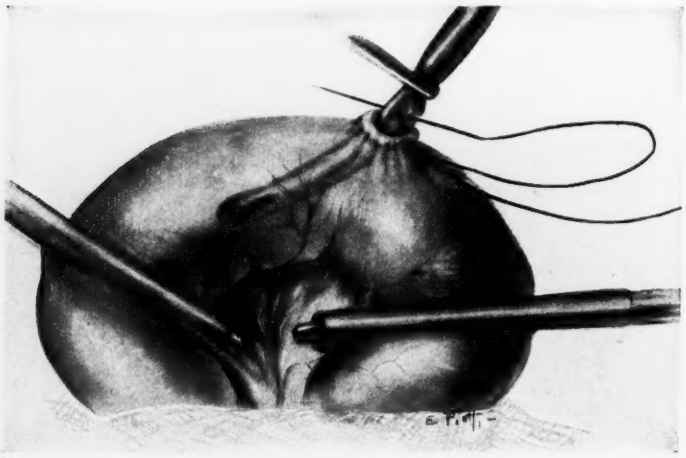

FIG. 2.—After the knot is tied in the first purse-string suture, the same thread is carried through the catheter to hold it in its position.

into the peritoneal cavity, and we have had no trouble with intestinal contents escaping to the surface of the abdominal wall and causing digestion of the skin. Perforation of the bowel by the tip of the catheter,[21] and the fear that the second purse-string might encroach upon the lumen of the bowel are complications which we have not encountered.

It has been said that the fistula may not close spontaneously when this technic is used. In 60 cases of enterostomy performed by this technic for

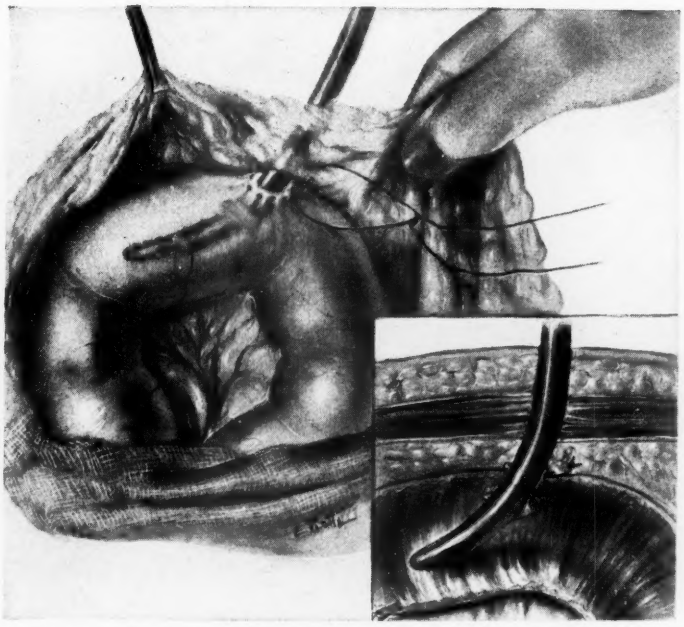

FIG. 3.—A second purse-string is placed around the catheter, which is pushed in as this is tied. This invaginates the intestinal wall. With the same suture, used for the second purse-string, the omentum is caught and tied down around the catheter. The insert shows, in cross-section, the relations of the invaginated bowel wall to the catheter, the omentum, and the abdominal wall.

various reasons during the past five years, there has never been a case in which the fistula did not close spontaneously. In cases in which jejunostomy was established for feeding purposes, there has been only a very slight amount of drainage for 18-36 hours after the catheter is removed. In a recent case in which jejunostomy was performed as a secondary operation for feeding purposes after a gastric resection, the catheter remained in the jejunum for 30 days. Following the removal of the catheter, there was no more than 15-20 cc. of drainage and the fistula closed without further drainage after 36 hours. We have encountered no cases of wound infection in these feeding cases, such as may happen when an enterostomy is performed for drainage purposes in instances of intestinal obstruction or peritonitis. One must be certain that enough time (at least 12 days) has elapsed to have a definite fistula established before removing the catheter.

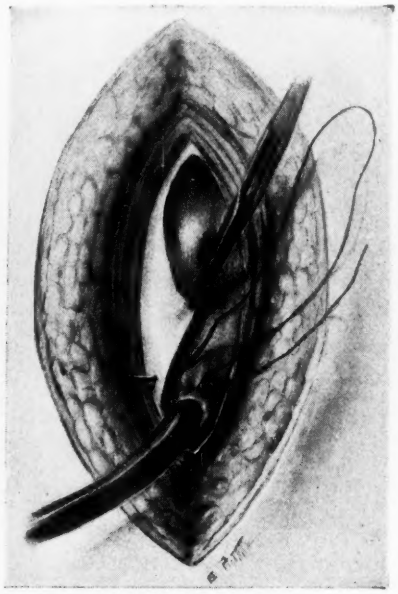

FIG. 4.—When no omentum is available for interposition between the bowel and the parietal peritoneum, the second purse-string suture is passed into the parietal peritoneum at the angle of the wound. This seals off the point of enterostomy.

CONCLUSIONS

(1) Malnutrition in surgical patients is widespread and of varying severity. Postoperative care, to-day, in surgical cases must continue the preoperative treatment of nutritional deficiency.

(2) Inadequate fluids, hypoproteinemia and vitamin deficiencies are especially common in surgical lesions of the upper gastro-intestinal tract. These can best be managed by supplying proper food through the gastro-intestinal tract.

(3) A simple jejunostomy at the time of operation provides a safe means for immediate administration of food and fluid, after operation, through the proper body channels.

(4) A description of the technic of the enterostomy, and a list of recent cases for which it was employed, is given.

BIBLIOGRAPHY

[1] Abbott, W. O., and Rawson, A. J.: A Tube for Use in the Postoperative Care of Gastro-enterostomy Patients. J.A.M.A., **112**, 2414, 1939.

[2] Allen, A. W.: Surgery of the Stomach. New England Jour. Med., **222**, 434–444, 1940.

[3] Barber, W. H.: Jejunostomy. ANNALS OF SURGERY, **79**, 553–576, 1933.

[4] Clute, H. M.: Factors Reducing Mortality in Acute Appendicitis. New England Jour. Med., **207**, 347–352, 1932.

[5] Clute, H. M., and Albright, H. L.: Total Gastrectomy for Cancer. Am. Jour. Surg., **35**, 56–63, 1937.

[6] Clute, H. M., and Mason, R. L.: Total Gastrectomy; Case Report. Tr. New Eng. Surg. Soc., **13**, 83, 1930.

[7] Coller, F. A., and Maddock, W. G.: Water and Electro'yte Balance. Surg., Gynec., and Obstet., **70**, 340–354, 1940.

[8] Downes, W. A.: Jejunostomy: Its Value in Treatment of Certain Ulcers of the Stomach and as a Palliative Measure in Inoperable Carcinoma of the Stomach. Surg. Clin. North America, **1**, 1619–1632, 1921.

[9] Evans, R. C.: Enterostomy in Intestinal Surgery. Am. Jour. Surg., **24**, 53–62, 1934.

[10] Golding-Bird, C. H.: Jejunostomy. Brit. Med. Jour., **2**, 1063–1064, 1885.

[11] Gould, P., and Lee, R. J.: Cancer of Pylorus and Duodenum; Jejunostomy; Death. Lancet, **2**, 1092–1093, 1885.

[12] Hawk, G. W.: Indications for Enterostomy with Special Reference to Technic. Penn. Med. Jour., **38**, 782–787, 1935.

[13] Heyd, C. G.: Jejunostomy. Am. Jour. Surg., **1**, 188–192, 1926.

[14] Hofmeister, F.: (Quoted by Linton) Zur Technik der Enterostomie. Verhandl. Gesell. Deutsch. Naturforsch. u. Artze, **77**, Pt. 2, **2** Hlfte., **95**, 1905.

[15] Holman, E.: Vitamin and Protein Factors in Preoperative and Postoperative Care of the Surgical Patient. Surg., Gynec., and Obstet., **70**, 261–269, 1940.

[16] Jones, C. M., and Eaton, F. B.: Postoperative Nutritional Edema. Arch. Surg., **27**, 159–177, 1933.

[17] Jones, C. M., Eaton, F. B., and White, J. C.: Experimental Postoperative Edema. Arch. Int. Med., **53**, 649–674, 1934.

[18] Jones, C. M.: Medical Aspects of Surgery of the Stomach and Duodenum. New England Jour. Med., **222**, 425–427, 1940.

[19] Judd, E. S., and Rankin, F. W.: Ileostomy Following Resection of the Colon. Surg., Gynec., and Obstet., **35**, 50–52, 1922.

[20] Kirschner, M.: Die prophylaktische Jejunostomie bei Magenoperationen. Arch. f. klin. Chir., **157**, 561–600, 1929.

[21] Klingenstein, P.: Perforation of Intestine Due to Enterostomy Tube. Jour. Mt. Sinai Hosp., **4**, 292–297, 1937.

[22] Lanman, T. H., and Ingalls, T. H.: Vitamin Deficiency and Wound Healing. ANNALS OF SURGERY, **105**, 616–625, 1937.

[23] Linton, R. R.: Enterostomy. Am. Jour. Surg., **25**, 55–63, 1934.

[24] Long, J. W.: Enterostomy: A Perfect Technic. J.A.M.A., **68**, 833–835, 1917.

[25] Mayo, W. J.: Jejunostomy. Am. Jour. Med. Sci., **143**, 469–473, 1912.

[26] Mayo, C. H.: The Cause and Relief of Intestinal Obstruction. J.A.M.A., **79**, 194–197, 1922.

[27] Mayo-Robson, A. W.: Jejunal and Gastrojejunal Ulcers. Brit. Med. Jour., **1**, 1–2, 1912.

[28] Mecray, P. M., Barden, R. P., and Ravdin, I. S.: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations. Surgery, **1**, 53–64, 1937.

[29] Mensing, E. H., and Kelley, E. H.: Total Suppression of Acid Gastric Secretion and Hunger Contractions by Means of Jejunostomy. Am. Jour. Surg., **20**, 99–101, 1933.

[30] Minot, G. R.: Harvard and Nutrition. New England Jour. Med., **215**, 1147–1149, 1936.

[31] Moynihan, B. G. A.: The Operation of Jejunostomy: Report of Two Cases. Brit. Med. Jour., **1**, 1599–1600, 1902.

[32] Payne, R. L.: Jejunostomy for Restoring Electrolytes Lost in Persistent Vomiting. Surg., Gynec., and Obstet., **60**, 880–882, 1935.

[33] Ravdin, I. S., Stengel, A., Jr., and Prushankin, M.: The Control of Hypoproteinemia in Surgical Patients. J.A.M.A., **114**, 107–112, 1940.

[34] Scott, H. G., Holinger, P. H., and Ivy, A. C.: Demonstration of a Dog Maintained for 16 Weeks Solely by Jejunal Alimentation in the Presence of Loss of Gastric Juice. Proc. Soc. Exper. Biol. and Med., **28**, 569–570, 1931.

[35] Scott, H. G., and Ivy, A. C.: Jejunal Alimentation. ANNALS OF SURGERY, **93**, 1197–1201, 1931.

[36] Stengel, A., Jr., and Ravdin, I. S.: The Maintenance of Nutrition in Surgical Patients; with a Description of the Orojejunal Method of Feeding. Surgery, **6**, 511–519, 1939.

[37] Taffel, M., and Harvey, S. C.: Effect of Absolute and Partial Vitamin C Deficiency on Healing of Wounds. Proc. Soc. Exper. Biol. and Med., **38**, 518–525, 1938.

[38] Thompson, W. D., Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption. Arch. Surg., **36**, 500–508, 1938.

[39] Walker, I. J.: Jejunostomy. Boston Med. and Surg. Jour., **186**, 108–111, 1922.

[40] Webber, I. M.: The Limitations of Enterostomy and Undesirable Effects Incident to Its Use. New England Jour. Med., **212**, 1–7, 1935.

[41] Weech, A. A., and Ling, S. M.: Nutritional Edema. Jour. Clin. Invest., **10**, 869–888, 1931.

[42] Weech, A. A., Snelling, C. E., and Goettsch, E.: The Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs. Jour. Clin. Invest., **12**, 193–216, 1933.

[43] Wesson, H. R.: Postoperative Gastric Retention Treated by Jejunostomy; Feeding. Proc. Staff Meet. Mayo Clinic., **12**, 747–751, 1937.

[44] Wolfer, J. A.: Jejunostomy with Jejunal Alimentation. ANNALS OF SURGERY, **101**, 708–725, 1935.

STUDIES ON THE USE OF METALS IN SURGERY

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PART I

COMPARATIVE DETERMINATIONS OF THE CYTOTOXICITY OF CERTAIN METALS IN FIBROBLAST CULTURE*

AN IDEAL METAL for use in bone surgery should be noncytotoxic, light, and so strong that the bulk of the appliance could be kept small. Its value would be still further enhanced if the physical properties were such that it not only cast well but existed in a malleable form, particularly if, in the latter state, it could be quickly hardened by heating.

A number of noncytotoxic metals and alloys are in existence, several of which are quite satisfactory for internal splinting of bone. Of these, stainless steel and Vitallium are perhaps two of the best examples. The latter has been carefully studied in both animals and man by Venable and his coworkers,[1, 2] who have convincingly demonstrated its usefulness. Our observations upon the effect of Vitallium upon the rate of growth of fibroblasts in tissue culture (see below), and, thus far, of its tolerance (in the form of plates) *in vivo*, afford further corroboration of its applicability in bone surgery.

If, at operation, the available appliance cannot be fitted satisfactorily, it would be very convenient to be able to alter its shape as desired, then quickly to harden it. This, so far as we have been able to learn, cannot be carried out with Vitallium, for it is not malleable.

While searching for a metal which would conform to the above-mentioned requirements, and which would be suitable for the repair of extensive cranial defects, our attention was called to a relatively new alloy, Ticonium. It is made up of nickel, cobalt, chromium, and molybdenum, with a small amount of beryllium added if it is to be cast. The physical properties† are quite

* A study of the use of various metals for the repair of cranial defects was undertaken at the same time, which will be published shortly.

† The metallurgic properties‡ of this alloy in its two different forms are:

(1) *Casting Alloy.*—This alloy, which is used in casting, has the following composition: Nickel 35.6 per cent, cobalt 29.1 per cent, chromium 27.7 per cent, molybdenum 6.0 per cent, beryllium 1.6 per cent. This metal has the lowest melting point of any alloy in the so-called chromium alloy series and, due to the presence of beryllium, can be cast to a high degree of fidelity. Its physical properties are as follows:

satisfactory—it is strong, rather light, and can be very accurately cast or wrought.

We have been studying the tolerance of Ticonium, by living tissues, and hence its applicability in surgery, both *in vitro* and *in vivo*. The present communication is an account of our observations of the effect of Ticonium, Vitallium, and other metals upon the growth of fibroblasts in tissue cultures. A subsequent report will record our studies of local tissue response to plates and screws in the dog's skull. The evidence thus far obtained, indicates that Ticonium, like Vitallium, silver, gold, and stainless steel, is not cytotoxic.

Method.—Ménégaux, Odiette, and coworkers[3, 4, 5, 6, 7, 8] have conclusively shown that the cytotoxicity of metals can best be studied in tissue cultures. Lately, the method of these authors has also been used by G. Krull,[9] and by A. H. Smook and Gaillard.[10]

The determination of the cytotoxicity of the metals, as carried out in the present study, is based upon the rate of growth of pure fibroblast cultures (obtained from the heart of a chicken embryo) in the presence of different metals. All these observations have been made on different generations of one and the same fibroblast strain. This strain was started February 21, 1940, and was discontinued June 21, 1940, in its forty-first generation. In order to assure growth of pure fibroblasts for actual determinations, we did not use any generations previous to the tenth generation.

Metal disks§ were prepared similar to those described by Ménégaux, Odiette, and Moÿse.[3] Each disk measured 1.5 Mm. in diameter, and 0.25

Rockwell hardness C 30; yield point 65,000–68,000 lbs. per sq. in.; ultimate strength 90,000–93,000 lbs. per sq. in.; elongation 6 per cent. The alloy may be heat treated if desirable to be hardened or softened. During the hardening treatment, the alloy is heated to 2,000° F., quenched, and then drawn to 1,300° F. The alloy then increases in hardness to Rockwell C 40–45 and the yield point also raises to 85,000–95,000 lbs. per sq. in. This alloy in the hardened condition is quite brittle. During the softening treatment, the alloy is drawn to 2,000° F. The alloy then softens to Rockwell C 18 and the yield point drops to about 45,000 lbs. per sq. in. In the softened condition, the alloy can easily be worked or machined if desired.

(2) *Wrought Alloy.*—The alloy which is used in wrought stock has the following composition: Nickel 36.2 per cent, cobalt 29.6 per cent, chromium 28.2 per cent, molybdenum 6.0 per cent. Its properties depend upon the amount of cold work done after the last anneal. For example, stock drawn to 50–60 per cent cold reduction in area after final anneal: Ultimate strength 237,000 lbs. per sq. in.; yield point 177,000 lbs. per sq. in.; elongation 6 per cent. Stock drawn to a 30 per cent cold reduction in area after final anneal: Ultimate strength 220,000 lbs. per sq. in.; yield point 183,000 lbs. per sq. in.; elongation 6 per cent. Stock drawn and fully annealed: Ultimate strength 150,000 lbs. per sq. in.; yield point 96,000 lbs. per sq. in.; elongation 31 inches on ten inches gauge length (52 per cent on two inches gauge length); hardness Rockwell B 95.

‡ The metallurgic data were made available by Mr. E. Touceda from the Touceda Laboratories, Albany, N. Y.

§ The metal disks were kindly prepared by the Touceda Laboratories in Albany, N. Y., and the Vitallium by the Austenal Laboratories in New York City.

Mm. in thickness. We have carried out our determinations on eight different metals, namely, gold, silver, Ticonium (casting alloy), Ticonium (wrought alloy), Vitallium, stainless steel, vanadium and copper.

Throughout the various experiments, we have compared the different metals with each other as well as with control cultures containing no metal. As an additional control, we have used cultures containing gold disks, as gold has proved to be nontoxic to fibroblast cultures (Ménégaux and associates[7]).

Technic.—Explants from the heart muscle of an 11-day-old chick embryo were prepared and cultivated by means of the hanging-drop technic. The medium used consisted of chicken plasma, chick embryo extract and Tyrode solution. The blood necessary for the preparation of the plasma was obtained under sterile precautions from young roosters by cardiac puncture. Heparin (1 mg. per 1 cc. saline) was used in order to prevent coagulation. The blood was then centrifuged for ten minutes at 2,300 R.P.M. After centrifuging, the supernatant plasma was withdrawn with pipettes. Small amounts of plasma were placed in previously autoclaved test tubes and stored in the refrigerator. Fresh plasma was prepared every two to three weeks.

For the preparation of embryonic tissue extract, eggs were incubated for eight or nine days at a temperature of 38.5° C. Twenty-four hours before the transplantation, the embryo was removed to a sterile watch-glass and reduced to a pulp by the use of a fine scissors. The undiluted pulp was then stored in the refrigerator. Immediately before the transplantation, the extract was centrifuged for ten minutes at 2,300 R.P.M. The supernatant fluid was withdrawn and mixed with Tyrode solution (3:0 dilution).

The Tyrode solution was prepared as described by Parker.[11] The *p*H of the solution was kept at 7.4–7.6. We have found that it is of the utmost importance to keep the *p*H at this level, for the rate of growth, as well as the type of growth, was influenced immediately whenever the *p*H was changed. The *p*H was checked colorimetrically at frequent intervals. The completed mixture was passed through a Seitz filter and was then stored in small amounts in the refrigerator in rubber-stoppered test tubes. For transplantation, each culture was divided into two or four approximately equal parts, and each part placed in a drop of plasma upon a new coverslip. One equal-sized drop of embryonic tissue extract, which had been mixed previously with Tyrode solution (3:1), was added and the hanging-drop culture sealed upon a round depression slide by the use of vaseline. As soon as coagulation had taken place, the cultures were placed in an incubator at a temperature of 38.5° C. Every two or three days these cultures were transferrd to a new medium until finally nothing but fibroblasts were growing. With the tenth generation we started our experiments. Each transplant of this generation was divided into four equal pieces. These pieces of tissue were implanted in a hanging-drop. A Ticonium disk was added to the first transplant, a gold disk to the second, a copper disk to the third, and the fourth transplant was cultivated without any metal. The disks were placed fairly close to the tissue (Figs.

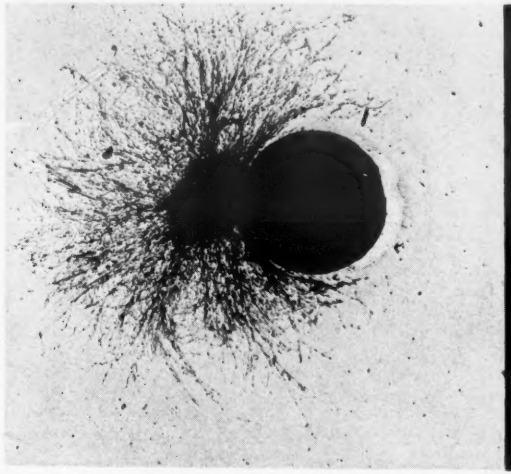

FIG. 1.—Fibroblast culture (thirty-eighth generation) in presence of a silver disk. (Hansen's hematoxylin stain. [×23])

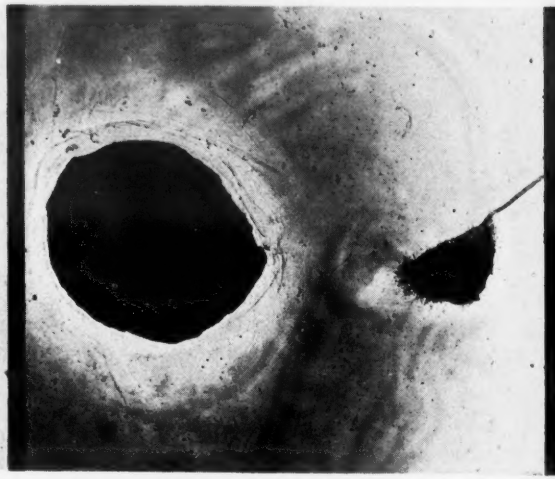

FIG. 2.—Fibroblast culture (eleventh generation) in presence of a copper disk. No growth. Note distance between transplant and copper disk. (Hansen's hematoxylin stain. [×34])

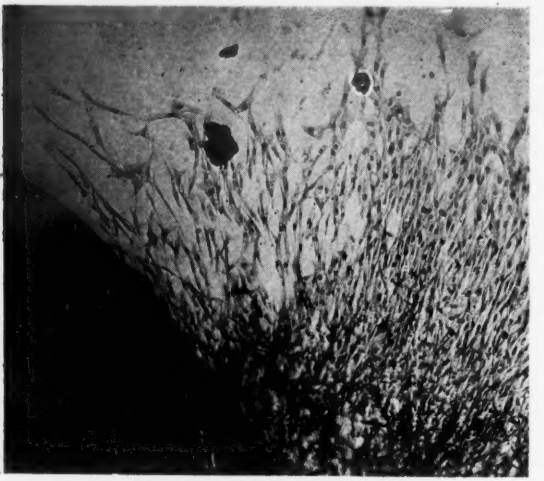

FIG. 3.—Section of fibroblast culture (eleventh generation) in presence of a Ticonium disk. A part of the disk is visible in the left lower corner. Note the growth of cells along the edge of the metal. (Hansen's hematoxylin stain. [×112])

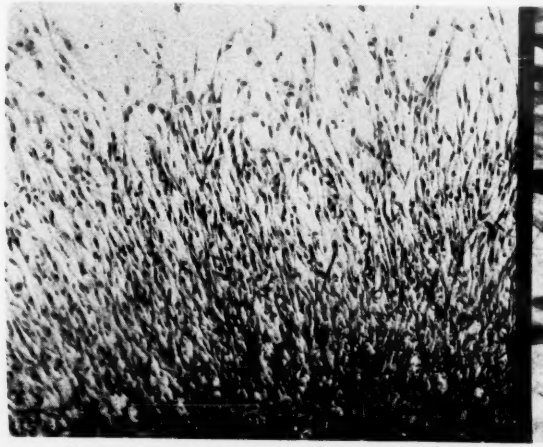

FIG. 4.—Section of fibroblast culture (eleventh generation) in presence of Ticonium disk. (Hansen's hematoxylin stain. [×112])

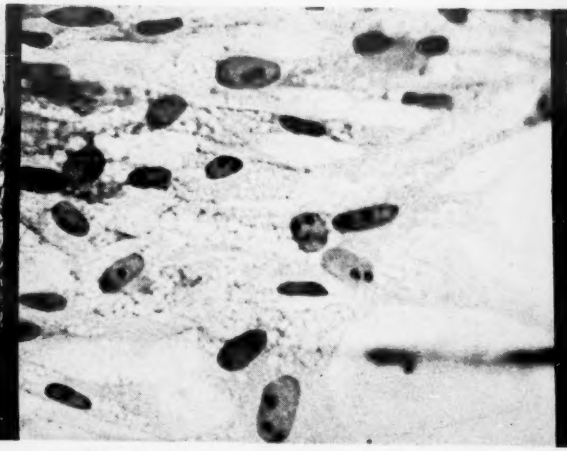

FIG. 5.—Section of fibroblast culture (eleventh generation) in presence of Ticonium disk. (Hansen's hematoxylin stain. [×880])

FIG. 6.—Section of fibroblast culture (thirty,third generation) in presence of Vitallium disk. (Hansen's hematoxylin stain. [×112])

1 and 3). After coagulation had taken place, the outline of each culture was drawn by use of the camera lucida and placed in the incubator immediately afterward. After exactly 48 hours, the cultures were again drawn by use of the camera lucida at the same magnification. Subsequent experiments were carried out in a similar manner.

By use of a planimeter, the area of the original fragment as well as the total area was measured. The absolute increase of the fragment was obtained by subtracting the area of the original fragment from the total area. The absolute increase of the fragment was then divided by the area of the primitive fragment, thus determining the relative increase of the fragment (Ebeling[12]). This value we have called the "factor of growth."

We realize that this method of surface measurements fails to take into consideration the growth in the third dimension; however, we have felt it to be of value to show these figures for they are a means of expressing all the significant variations which we have seen in this comparative study of cytotoxicity.

TABLE I

ELEVENTH GENERATION

	Relative Increase of the Fragment in the Presence of:			
	Ticonium (casting alloy)	Gold	Copper	Control
	11.00	11.00	0.00	14.90
	8.87	4.16	....	12.00
	5.81	9.10	....	7.97
	14.80	7.80	0.00	13.10
	.....	6.00	0.00	9.90
	12.40	9.40	0.00	11.70
	13.40	11.60	....	14.00
	.....	10.70	....	9.00
	4.20	7.40	....	6.30
Averaged Factor	**10.07**	**8.57**	**0.00**	**10.98**
Maximum	*+4.73*	*+3.03*	....	*+3.92*
Minimum	*−5.87*	*−4.41*	....	*−4.68*

TABLE II

THIRTY-THIRD GENERATION

	Relative Increase of the Fragment in Presence of:			
	Ticonium (wrought alloy)	Vitallium	Vanadium	Control
	7.8	5.1	0.00	5.3
	8.2	6.6	0.00	6.8
	7.4	7.0	0.00	6.8
	10.1	9.1	....	...
	10.6	...	....	...
	15.1	...	....	...
Averaged Factor	**9.9**	**7.0**	**0.00**	**6.3**
Maximum	*+5.2*	*+2.1*		*+0.5*
Minimum	*−2.5*	*−1.9*		*−1.0*

Experiments.—In every experiment, the average factor of growth of the fibroblast cultures for each metal was calculated. Table I shows the growth factors of the fibroblast cultures in their eleventh generation; Table II, those of the cultures in their thirty-third generation.

Of the 41 generations, 13 generations were chosen for our determina-

tions. A total of 222 fibroblast cultures have been examined; 31 control cultures without any metal disks have been examined and measured; gold was tested in 24 cultures; silver in 21; Ticonium (casting alloy) in 40; Ticonium (wrought alloy) in 31; Vitallium in 13; stainless steel in 23; vanadium in 21 and copper in 18 cultures.

The average factor of growth of the fibroblast cultures for each metal, as obtained from the different generations, used thus for study, is summarized in Table III.

TABLE III

AVERAGE OF THE RELATIVE INCREASE OF THE FRAGMENT ("FACTOR OF GROWTH")

Generation	No. of Cultures	Ticonium (cast)	Ticonium (wrought)	Gold	Silver	Vitallium	Stainless Steel	Vanadium	Copper	Control
11, a	29	10.07	..	8.57	..	..	..	..	0.00	10.98
11, b	13	8.60	..	8.50	..	..	..	..	..	..
15	14	10.80	..	9.40	..	..	..	..	..	..
18	4	..	..	..	..	..	..	0.00	..	7.74
19	16	..	5.70	..	..	..	..	..	..	5.70
25	30	6.00	..	..	..	..	8.93	1.80	..	..
26	16	..	6.40	9.20	..	..	6.34	..	..	..
28	13	..	24.10	..	..	..	8.90	0.00	0.00	..
29	15	7.50	8.90	..	..	..	..	..	0.00	..
33	16	..	9.90	..	..	7.00	..	0.00	..	6.30
38	21	..	..	..	8.90	..	..	..	..	8.00
39	19	..	7.05	..	8.94	..	5.28	1.77	..	..
41	15	..	23.18	..	13.00	16.49	..	..	..	..
Averaged Factor		**8.59**	**9.31**	**8.91**	**10.28**	**11.74**	**7.36**	**0.71**	**0.00**	**7.74**
Maximum		*+2.21*	*+14.79*	*+0.40*	*+2.72*	*+4.45*	*+1.57*	*+1.09*		*+3.24*
Minimum		*−2.59*	*− 3.61*	*−0.41*	*−1.38*	*−4.74*	*−2.08*	*−0.71*		*−2.04*

A number of cultures were fixed in neutral Ringer-formol solution (Parker[11]), and have been stained with Hansen's hematoxylin (Figs. 1, 2, 3, 4, 5, 6) for purpose of illustration.

Before we started the strain used for the evaluations given above, we studied the influence of different metals upon the rate of growth of about 200 fibroblast cultures, which were discarded after observation. The results of these single experiments correspond with our findings obtained from the strain described above.

(1 *Control Cultures.*—For five different generations we prepared a total of 31 cultures, cultivated without any metal disk in the medium. Table III shows the average factors of growth for the different generations. The average factor of growth for all 31 cultures was calculated to be 7.74. It is well-correlated with the factors obtained for those metals that we will show to be nontoxic. The difference between these control cultures and the two toxic metals (vanadium and copper) in our series is obvious.

(2) *Gold and Silver.*—As stated above, for five different generations, we prepared a total of 31 cultures without any metal disk. In the remaining eight generations, we have used metals as controls, for instance, gold which has been proved to be noncytotoxic (Ménégaux and Odiette[7]). We thought that it would be interesting to compare the growth in the presence of these

nontoxic metals with the growth in the presence of those metals which we have been investigating for their possible use in surgery.

For four generations we cultivated fibroblasts in the presence of gold disks. This represented a total of 24 cultures. The average of the relative increase of the fragment amounted to 8.91. Silver disks were implanted in 21 cultures belonging to three different generations. The average factor of growth amounted to 10.28.

(3) *Ticonium.*—For five generations we prepared cultures with the "casting alloy" Ticonium, representing a total of 40 fibroblast cultures. The factor of growth averaged 8.59. The factor of growth for the "wrought alloy" Ticonium was 9.31. It was obtained from a total of 31 cultures studied in seven different generations.

(4) *Vitallium.*—Thirteen cultures were used for testing the alloy vitallium. These 13 cultures were chosen from only two different generations. In the thirty-third generation the average factor of 7.00 was obtained (Table II). For the forty-first generation, the factor for Vitallium was 16.49. In the forty-first generation, however, the factor for silver was 13 while that of the "wrought alloy" Ticonium was 23.18.

The fibroblast cultures for this generation obviously grew luxuriantly, thus raising the average factor of growth above the level obtained in other experiments. That the average area of growth for Vitallium amounted to 11.74, may be explained by the fact that Vitallium was tested in this generation and in one other only, whereas the "wrought alloy" Ticonium was tested in seven different generations.

(5) *Stainless Steel.*—This metal was tested in a total of 23 cultures obtained from four different generations. The average factor was 7.36.

(6) *Vanadium.*—Twenty-one cultures were tested with Vanadium in five different generations. Thirteen of these cultures did not grow at all. The remaining eight showed a marked inhibition of growth, the average factor of growth was 0.71. Clinically, the failure of this metal has been reported repeatedly. We have now obtained proof *in vitro* for the high cytotoxity of this alloy.

(7) *Copper.*—Copper was tested in three different generations with a total of 18 cultures. None of these cultures showed any growth of fibroblasts.

Discussion.—The evaluation given above draws a definite line between the six nontoxic metals and vanadium and copper, both of which prove to be highly cytotoxic. We have based our determinations on one criterion—the actual growth of fibroblasts in the presence of metals.

Copper in its pure form may be considered completely cytotoxic, since no growth was obtained in any of the cultures containing it. Vanadium may be regarded somewhat less cytotoxic than copper, for a slight growth was obtained in eight of 21 cultures and no growth at all in the remaining 13. The cytotoxicity of vanadium in our cultures is of such a degree as to make the

use of this substance in bone surgery inadvisable. Its cytotoxicity is the probable explanation of the failures reported of its use in clinical surgery.

Five of these substances (gold, silver, Vitallium, and two Ticonium compounds) gave a factor of growth higher than the control cultures without metal disks. Stainless steel gave a result slightly higher than the controls without disks.

We do not feel that any conclusive deductions can be drawn from the varying rates of growth of the metals we have found to be noncytotoxic.

SUMMARY

(1) The cytotoxicity of the eight metals (gold, silver, Ticonium (casting alloy), Ticonium (wrought alloy), Vitallium, stainless steel, vanadium, and copper) was determined by measuring the area of growth of fibroblast cultures in the presence of these metals.

(2) Gold, silver, Ticonium (casting alloy), Ticonium (wrought alloy), Vitallium and stainless steel are found to be nontoxic. Vanadium and copper are found to be highly cytotoxic.

The authors wish to express their appreciation to Dr. Joseph Schwind of the Department of Anatomy, for his help and advice in this work, and to Mr. E. G. Touseda for his interest in the metallurgic phase of the study. Mr. John Ziegler also rendered valuable assistance.

REFERENCES

[1] Venable, C. S.: Osteosynthesis in the Presence of Metals. Jour. South. Med. Assn., **31**, 5, May, 1938.

[2] Venable, C. S., Stuck, W. G., and Beach, A.: The Effects on Bone of the Presence of Metals; Based upon Electrolysis. Tr. South. Surg. Assn., **49**, 294, 1936.

[3] Ménégaux, G., Odiette, D., and Moÿse, P.: Action de quelques métaux simples sur la croissance des fibroblastes *in vitro*. Presse méd., **42**, 7, 1934.

[4] Ménégaux, G.: Croissance des tissus conjonctif et osseux cultivés *in vitro* en présence de certains métaux. Presse méd., **42**, 658–662, 1934.

[5] Ménégaux, G.: Action cytotoxique de quelques métaux sur le tissu osseux cultivé en vie relentie. Presse méd. **42**, 1844–1848, 1934.

[6] Ménégaux, G., and Odiette, D.: De l'action des differents métaux sur le tissu osseux. Jour. de Chir., **46**, 695–726, 1935.

[7] Ménégaux, G.: Action cytotoxique de certains métaux sur des ostéoblastes humains cultivés *in vitro*. Presse méd., **43**, 1555–1557, 1934.

[8] Ménégaux, G.: Influence des métaux couplés sur la croissance des cultures *in vitro* de fibroblastes et d'ostéoblastes. Compt. rend. Soc. de biol., **119**, 485–487, 1935.

[9] Krull, G.: Untersuchungen über die Giftigkeit rostfreien Stahles in der Gewebskultur. Arch. f. orthrop. und Unfallchir., **37**, 600–605, 1937.

[10] Smook, A. H., and Gaillard, P. J.: Über den Einfluss verschiedener Metalle auf Knochengewebe. Bruns' Beiträge zur klin. Chir., **170**, 3, 362–379, 1939.

[11] Parker, R. C.: Methods of Tissue Culture. P. C. Hoeber, Inc., New York, 1939.

[12] Ebeling: Measurement of the Growth of Tissues *in vitro*. Jour. Exp. Med., **34**, 231–243, 1921.

BOOK REVIEW

TREATMENT OF CANCER AND ALLIED DISEASES. Edited by GEORGE T. PACK, M.D., Attending Surgeon, Memorial Hospital, New York, N. Y., and EDWARD M. LIVINGSTON, M.D., Assistant Attending Surgeon, Memorial Hospital, New York, N. Y. New York and London: Paul B. Hoeber, Inc., 1940.

THIS THREE VOLUME WORK, prepared by 147 international authors, and consisting of 2,595 pages and 1,500 illustrations, is an amazing accomplishment, and the publishers as well as the authors have reason to be proud of the result. The binding, the paper, the type are superfine, and the uniformity of excellence of the enormous number of illustrations, supplied by nearly 150 authors, is almost unbelievable.

The work is in no sense confined to the special subject of cancer, but is a veritable encyclopedia of general surgery, and properly so, for there is no organ or tissue immune to cancer. In all the lesions some form of surgery is usually employed in addition to radiation and chemotherapy, and in the treatment of them an intelligent consideration of the diagnosis, the risk of operation, the pre- and postoperative care, the social and economic problems are all so vital that the scope of an encyclopedia of medicine is almost necessary. At least the authors have so approached this problem.

The consideration of the lesions as they involve special tissue and organs makes the subject matter readily available, and the vast experience of the authors guarantees a statistical value far above that which can be credited to many of the publications now in our surgical literature. Volume I contains 52 chapters devoted to lesions of the head, face, neck, breast and chest, while volume II, consisting of 42 chapters, is concerned with lesions of the esophagus, gastro-intestinal tract, and female genitalia. Volume III has 47 chapters, in which the lesions of the urinary system, male genitalia, skin, nervous system, bones, joints, lymphatic system, and such miscellaneous subjects as anesthesia, experimental therapy and nursing care are considered.

To surgeons, the detailed presentation of the operative technic, and the unusual quality of the illustrations provide an "Operative Surgery" which is not surpassed in English literature at the present time.

At the end of each chapter is a bibliography which has been selected with unusual discrimination, and there is a subject index in each volume averaging some 35 pages.

When one realizes the time required to prepare the manuscript, to which must be added that required to put it into proof, the readers will be amazed how up to date is the subject matter. This is well shown by a discussion of our recent concepts of water and electrolytic balance in the pre- and postoperative patient. This work is one that will be an asset to the library of every surgeon, as well as to those specializing in the care of cancer.

WALTER ESTELL LEE, M.D.

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